Article

Not peer-reviewed version

Multicomponent synthesis of 4-aryl-4,9-dihydro-1H-pyrazolo[3,4-b]quinolines using L-proline as a catalyst – does it really proceed?

Andrzej Danel *, Elżbieta Porębska, Kacper Markiel, Oleksii Havrysh, Mateusz Kucharek, Arkadiusz Gut, Tomasz Uchacz

Posted Date: 5 October 2023

doi: 10.20944/preprints202310.0271.v1

Keywords: 4-Aryl-4,9H-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]quinoline, multicomponent reactions, L-proline, 4,4-(phenylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-oles).

Article

Multicomponent Synthesis of 4-Aryl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinolines Using L-Proline as a Catalyst—Does It Really Proceed?

Andrzej Danel [1,*], Elżbieta Porębska [1], Kacper Markiel [1], Oleksii Havrysh [1], Mateusz Kucharek [2], Arkadiusz Gut [3] and Tomasz Uchacz [3]

[1] Faculty of Materials Engineering and Physics, Krakow University of Technology, Podchorążych Str.1, Krakow, Poland
[2] Faculty of Food Technology, Agricultural University, Balicka Str. 122, Krakow, Poland
[3] Faculty of Chemistry, Jagiellonian University, Gronostajowa Str. 2, Krakow, Poland
* Correspondence: rrdanela@cyf-kr.edu.pl

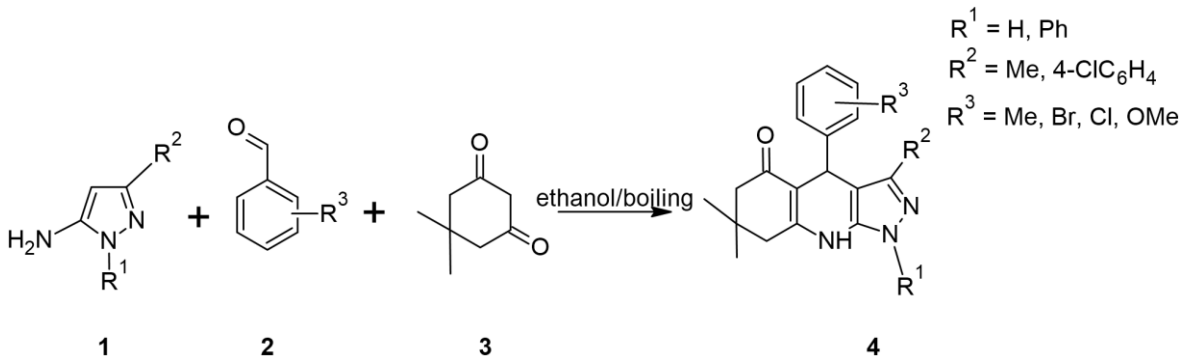
Abstract: Looking for effective synthetic methods for 1*H*-pyrazolo[3,4-*b*]quinolines preparation, we came across a procedure where in a three component reaction catalyzed by L-proline, 4-aryl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinolines are formed. These compounds can be easily oxidized to a fully aromatic system, which gave hope for a synthetic method that could replace e.g. Friedländer condensation, often used for this purpose, although severely limited by the availability of suitable substrates. However, after careful repetition of the procedures described in the publication, it turned out that the compounds described therein do not form at all. The actual compounds turned out to be 4,4-(phenylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-oles). 4-Aryl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinolines were prepared by another method and used as standards to compare the products formed in the original procedure.

Keywords: 4-Aryl-4,9H-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]quinoline; multicomponent reactions; L-proline, *4,4-(phenylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-oles)*

1. Introduction

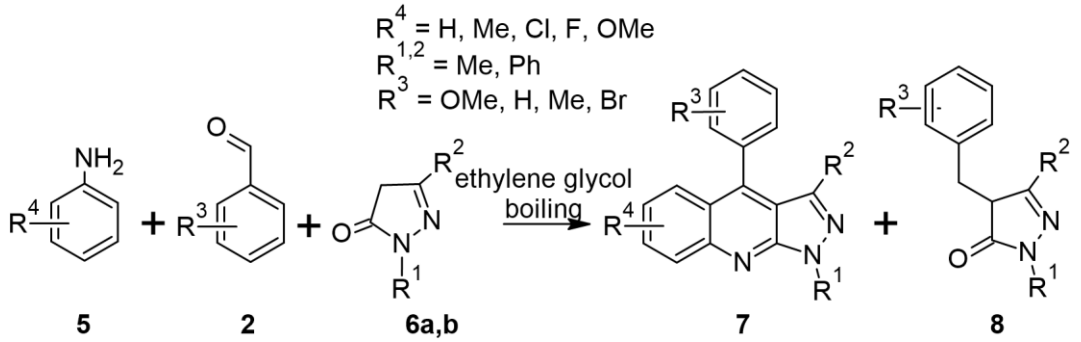
In 1901, Richard Willstätter synthesized tropinone, a synthetic precursor to the tropane alkaloid atropine. Its application, not always in a positive aspect, dates back to ancient times and is currently used, among others, in ophthalmology and as an antidote in case of organophosphate or organophosphorus compounds poisoning, e.g. parathion, tabun or sarin. The aforementioned tropinone was obtained in a 21-step synthesis from cyclopentanone with an overall yield of 0.75% [1] Hence, from a practical point of view, this reaction is basically useless. The opposite of this synthesis is the work published in 1917 by Robert Robinson, who obtained the mentioned tropinone in a one-step, three-component reaction with a yield of 17% [2]. This synthesis is one of the pioneering multicomponent chemical reactions. Earlier reactions of this type include Strecker's synthesis of amino acids from aldehydes, ammonia and hydrogen cyanide published in 1854, or the slightly later Mannich reaction [3,4]. Almost 150 years have passed since then and multi-component reactions have entered the canon of organic synthesis and have been used, among others, in for obtaining biologically active systems. The subject of multicomponent syntheses has been discussed in numerous reviews and is also presented in many monographs [5–8]. The 1*H*-pyrazolo[3,4-*b*]quinoline, which is the subject of research in the current publication, can also be obtained using multi-component reactions. Only some of them will be mentioned, because an exhaustive discussion of this topic was made in a review covering the last 100 years of syntheses of this nitrogen heterocyclic system [9]. The first reaction of this kind was described in 1998 by Hormanza *et al.* (Scheme 1) [10].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 October 2023 doi:10.20944/preprints202310.0271.v1



Scheme 1. The first three component synthesis of 1*H*-pyrazolo[3,4-*b*]quinolines.

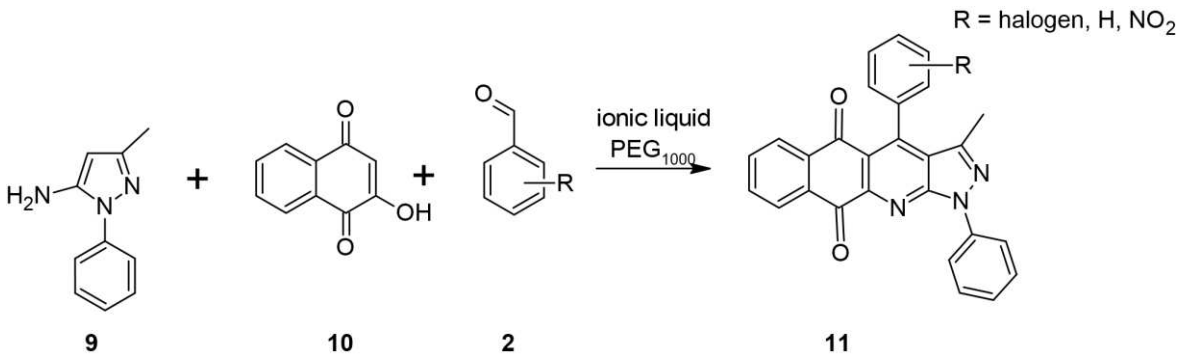
They used 1,3-disubstituted 5-aminopyrazole **1** , aromatic aldehyde **2**, and dimedone **3** for this purpose. During boiling in ethanol, formation of the corresponding 1*H*-pyrazolo[3,4-*b*]quinoline **4** was observed, in which both the carbocyclic ring and the middle one were not aromatic. Another important multicomponent reaction leading to 4-aryl-1*H*-pyrazolo[3,4-*b*]quinolines **7** is the procedure described by Tomasik *et al*. [11]. The authors used substituted anilines **5**, aromatic aldehyde **2** and 2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-5-one (**6a**, $R^{1,3}$ = Ph) or 2-phenyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**6b**, R^1 = Ph, R^2 = Me) (Scheme 2).



Scheme 2. The three component synthesis of fully aromatic 1*H*-pyrazolo[3,4-*b*]quinolines.

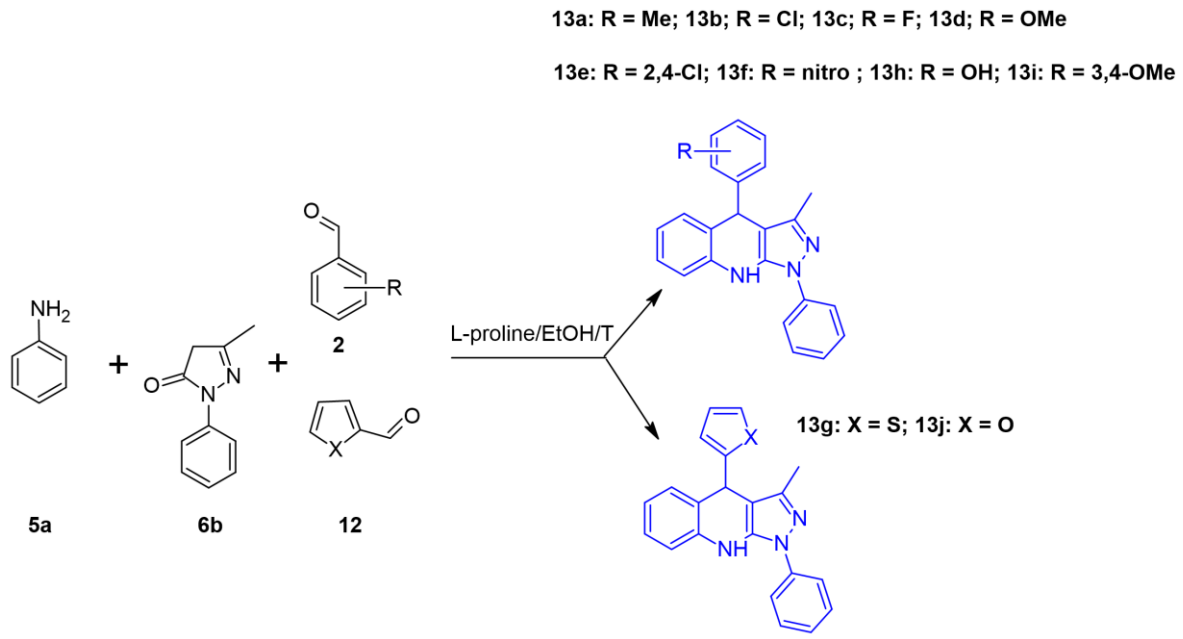
In this case a fully aromatic product is obtained. The reported yields, however, did not exceed 33% and even less when aniline was used. In the last case the final yields were less than 20%. The authors of the publication did not investigate the mechanism of formation of pyrazoloquinoline **7**, which takes place in the case of this reaction. Product **7** was easily isolated by treating the reaction mixture with methanol and sonicating the whole. Besides **7** benzal derivative **8** was also isolated. At present, this is the only example of this type of multicomponent reaction where 1*H*-pyrazolo[3,4-*b*]quinoline **7** system is formed. In other cases, compounds with an aromatic pyridine ring and a saturated carbocyclic system are obtained. An example of such a reaction is shown in Scheme 3, where 5-amino-3-methyl-1-phenylpyrazole **9**, 2-hydroxy-1,4-naphthalenedione **10** and aromatic aldehyde **2** were used. The reaction was carried out in the presence of an ionic liquid and PEG_{1000} and led to formation derivatives **11** [12,13].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 October 2023 doi:10.20944/preprints202310.0271.v1



Scheme 3. The three component synthesis of 1*H*-pyrazolo[3,4-*b*]quinolines with aromatic pyridine moiety.

In recent years, many multi-component reactions using L-proline as a catalyst have been described. These reactions, carried out under mild conditions, using water or alcohol as a solvent, are used, among others, for the synthesis of heterocyclic systems [14–17]. In 2017, Hegde and Shetty published a paper "*Facile one-pot multicomponent synthesis of 1H-pyrazolo[3,4-b]quinolines using L-proline as a catalyst*" in the Chemistry of Heterocyclic Compounds [18]. They used a three-component mixture of aniline **5a**, aromatic aldehyde **2/12**, 2-phenyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one **6b** and L-proline as a catalyst. The reaction was carried out in a boiling alcohol for 3-5 hours (Scheme 4).



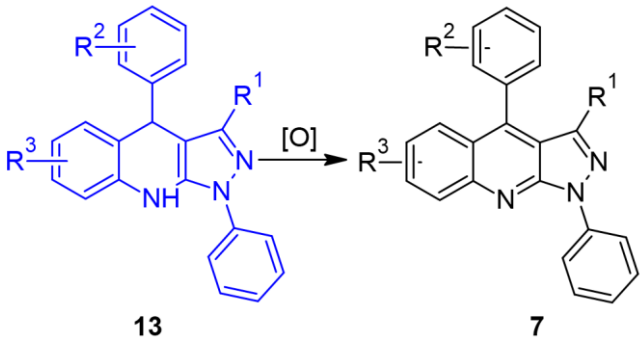
Scheme 4. The potential synthesis of 4-aryl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinolines **13**.

The aforementioned publication describes a series of eight 4-aryl-4,9-dihydro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinolines **13a-f, h, i** with an aromatic carbocyclic ring and two with a heterocyclic **13g, j** in the 4-position, which has not been found in the reactions reported so far. The final yields were also relatively high, reaching 78-89%.

2. Results and Discussion

The reaction published in the paper by Hedge and Shetty seemed to us very interesting because the obtained compounds **13** can be oxidized to give fully aromatic systems **7** (Scheme 5).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 October 2023 doi:10.20944/preprints202310.0271.v1

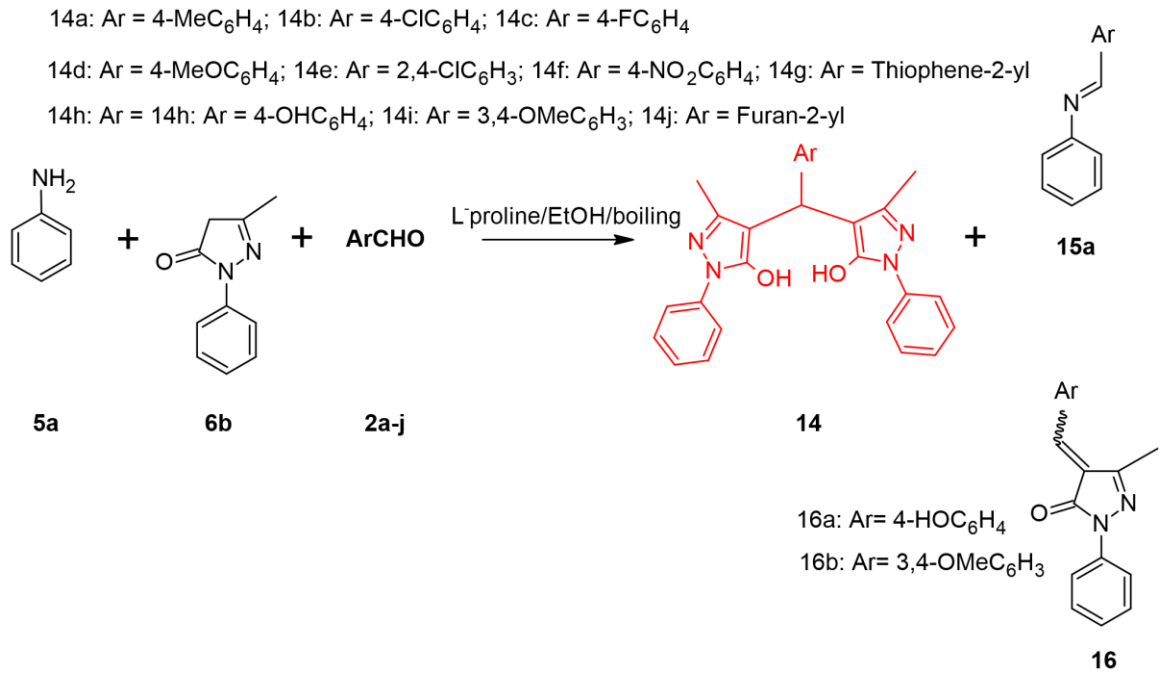


Scheme 5. Potential oxidative aromatization of 4-aryl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinolines.

An example of such reaction is the oxidation of pyrazolines to pyrazoles, which can be performed *e.g*. with oxygen in acetic acid, manganese(IV) oxide, DDQ or other oxidants [19–21]. Moreover, it can be expected that the overall yield could be greater than 33%, which is a serious shortcoming of the previous reaction described by Tomasik, especially in the case of aniline. For this reason, the reactions presented in Scheme 4 were very interesting to us and we decided to use their potential when it comes to the synthesis of fully aromatic 1*H*-pyrazolo[3,4-*b*]quinolines. The target was fluorescent sensors based on 1*H*-pyrazolo[3,4-*b*]quinolines substituted with a phenyl group in the 4-position. In 2001, Rettig and co-workers studied such sensors in which an aza-crown unit was used attached to the pyrazoloquinoline backbone through the phenyl group in position 4 [22]. 4-Aryl substituted pyrazolo[3,4-*b*]quinolines **7** can be synthesized using the Friedländer condensation of the corresponding *o*-aminobenzophenone and pyrazolone [23]. However, this route is out of the question for the synthesis of Rettig's sensors due to problems with the preparation of the corresponding *o*-aminobenzophenone attached to aza-crown moiety. Also, the conditions under which the Friedländer condensation is carried out in the case of 1*H*-pyrazolo[3,4-*b*]quinolines could lead to partial decomposition of the final compound. The reaction described by Tomasik *et al* is not suitable for preparing compounds in which the phenyl ring in the 4-position is substituted with amino groups. For this reason, the three-component reaction catalysed with L-proline and subsequent oxidation offered hope for potential success. Before it was decided to use appropriate aldehydes with chelating units, we selectively checked the results published by Hegde and Shetty. *p*-Tolualdehyde **2a**, *p*-chlorobenzaldehyde **2b** and 2,4-dichlorobenzaldehyde **2e** were selected for the tests. We chose these three compounds, among others, because the authors included spectra data of resulted 4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinolines **13a,b,e** in supplementary materials in the form of graphics. In the publication, the reaction was carried out on a scale of 1 mmol and after its completion the reaction mixture was poured into ice water, the resulted precipitate was filtered off and crystallized from ethyl acetate. In our case, we increased the scale to 5 mmol to facilitate the isolation procedure of the final product. We also noticed that after a few minutes of heating, precipitation occurs in the three pilot reactions mentioned above. The authors of the publication do not mention this phenomenon in the experimental part. Isolating products in such a case is very easy and is limited to filtering the precipitate and standard crystallization to obtain product for basic analyses. The yields of resulted three products were high, so we hope to have sufficient amount of starting material for further oxidation. In order to confirm the structure of the molecules obtained, we performed ^{1}H NMR and ^{13}C NMR analyses. Unfortunately it turned out that the obtained compounds were not 4-aryl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinoline **13a,b,e** derivatives at all. Instead, only 4,4'-(arylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-oles **14a**,**b**,**e** reaction products of an aromatic aldehyde **2** with two molecules of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazole-3-one **6b** were isolated (Scheme 6). Unfortunately, exactly the same situation happened when we repeated the reaction with other aldehydes **2c,d,e,f,g**. When *p*-hydroxybenzaldehyde **2h** and 3,4-dimethoxybenzaldehyde **2i** were reacted under the conditions described by Hegde and Shetty the orange precipitates **16a** and **16b** were isolated as products. Increasing the amount of solvent led to the formation of appropriate 4,4'-

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 October 2023 doi:10.20944/preprints202310.0271.v1

(arylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-oles **14i** and **14j** again. In the case of 2-furylaldehyde, we were unable to isolate any products from the post-reaction mixture due to its tarnation, even though we used freshly purified aldehyde. In addition, in the case of *p*-tolualdehyde, Schiff's base **15** (Ar = C_6H_4Me) was isolated from the post-reaction mixture. The compound was identified by comparison with a separately synthesized Schiff base prepared from aniline and *p*-tolualdehyde [24]. Appropriate Schiff bases were also detected with TLC in the post-reaction mixtures in the other two cases. The reactions were carried out exactly according to the procedures described in the publication, and also modified by extending the heating time to 24 hours with the same result. What is more interesting, when we carried out these reactions without the use of L-proline, we obtained exactly the same products **14**. So there is a clear conclusion that L-proline has no part in this reaction and certainly does not contribute to the formation of 4-aryl-4,9-dihydro-1*H*-pyrazolol[3,4-*b*]quinoline **13** at all. In the original publication, the authors proposed a potential mechanism for this reaction, with emphasis on the role of L-proline forming an enamine with 2-phenyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one **6b** at the first step. In the next turn the formed enamine reacts with an aldehyde and aniline at last leading to **13**. To finally remove any doubts about the product obtained by Hegde and Shetty, we performed additional syntheses by heating the pyrazolone **6b** and a few aldehydes namely **2a, 2i** and **2j** in a 2:1 molar ratio. The obtained compounds are known and described in the literature, hence there are no doubts about their structure. When we compared the R_f values of the products obtained in the reaction with L-proline, without L-proline and without aniline using TLC chromatography, it turned out that they were identical. In conclusion, 4-aryl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinolines **13a/b** were not formed in a three component reaction at all even though data from elemental analyzes and one based on MS spectra for **13b** indicate this.



Scheme 6. The synthesis of 4,4'-(arylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-oles) **14.**

In the reactions depicted in Scheme 6 red-orange 4-arylidene systems **16** are formed in the initial stage. These compounds disappear during the course of the reaction and are present in trace amounts in the post-reaction mixture (comparison by TLC with original samples of **16**). As the reaction proceeds, the corresponding 4,4'-(arylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ols) **14** precipitates in majority of cases or after the cooling in the refrigerator. As mentioned earlier the two exceptions were reactions with *p*-hydroxybenzaldehyde **2i** and 3,4-dimethoxybenzaldehyde **2j**, where instead of product **14**, 4-benzylidene derivatives **16 a/b** were obtained. They were formed at the very beginning of the reaction and did not disappear up to the end of heating. The disussion

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 October 2023 doi:10.20944/preprints202310.0271.v1

concerning the mechanism of this reaction can be found in the paper written by Hennig *et al*. [25] If we analyze the ^{1}H NMR spectra included in the publication of Hegde and Shetty, they have a common element, namely peaks in the range of 14.00-13.00 and approximately at 5 ppm. The authors attribute the first of them to the proton bounded to nitrogen in position 9 and the second one to the methine proton at carbon C-4. The collected data are included in Table 1. We have also included some ^{1}H NMR data for the derivatives **14** collected on the basis of some literature resources [26–28]. An example of such a publication is the work of Mohammadi and Ghorbani-Choghamarani who synthesized **14** (R= 4-Me, 4-Cl) using magnetic nanocomposites modified with sulfone groups [29]. If we take into account the ^{1}H NMR shift values of protons attached to nitrogen in position 9 for *p*-tolubenzaldehyde and *p*-chlorobenzaldehyde derivatives **13**, they are 14.00 and 13.90 ppm, respectively [18]. The corresponding shift values of the methine protons at the C-4 position are 4.89 ppm and 4.96 ppm. When we compare these values with the data published in Mohammadi and Ghorani-Choghamarani paper, we notice that they are almost identical, except that the values at the 13.94 ppm and 13.89 ppm correspond to protons attached to oxygen atoms of **14** and not nitrogen N-9 atoms in **13**. In the ^{1}H NMR spectra included in the work by Hegde and Shetty, one can also notice very weak broad peaks in the region of 12-13 ppm, which are identical to the peaks at 12.44 and 12.53 ppm coming from hydrogens associated with oxygen. In some derivatives 14 these peaks are not always visible.

Table 1. ^{1}H NMR data of 4-aryl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinolines **13** and 4,4′-(arylenemethylene)-bis-(3-methyl-1-phenyl-pyrazol-5-oles) **14.**

Ar	**4-Aryl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinoline 13 [18]**		**4,4′-(Arylenemethylene)-bis-(3-methyl-1-phenyl-pyrazol-5-ol) 14**	
	N-H	C-H	O-H	C-H
MeC_6H_4-	**14.00**	**4.89**	**13.94**; 12.44	**4.92** [29]
ClC_6H_4-	**13.90**	**4.96**	**13.89**; 12.53	**4.98** [29]
FC_6H_4-	13.92	4.77	13.70	4.94 [26]
$MeOC_6H_4$-	13.92	4.96	13.89	5.09 [26]
2,4-ClC_6H_3-	**13.93**	**5.09**	**13.95**; 12.67	**5.05** [32]
$NO_2C_6H_4$-	13.03	4.96	13.90; 12.49	5.14 [32]
3,4-$OMeC_6H_3$-	13.92	4.89	14.11; 11.68	4.91 [28]
4-OHC_6H_4	13.92	4.98	13.96; 12.2	4.86 [27]
Thiophen-2-yl	**13.91**	**4.96**	14.01; 12.51	**5.14** [29]
Furan-2-yl	13.89	4.96	13.24	5.01 [26]

In the Figure 1 we included a ^{1}H NMR spectrum of 4,4′-(4-chlorophenylmethylene)-bis-(3-methyl-1-phenyl-pyrazol-5-ole) **14b** and these two peaks can be seen.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 October 2023 doi:10.20944/preprints202310.0271.v1

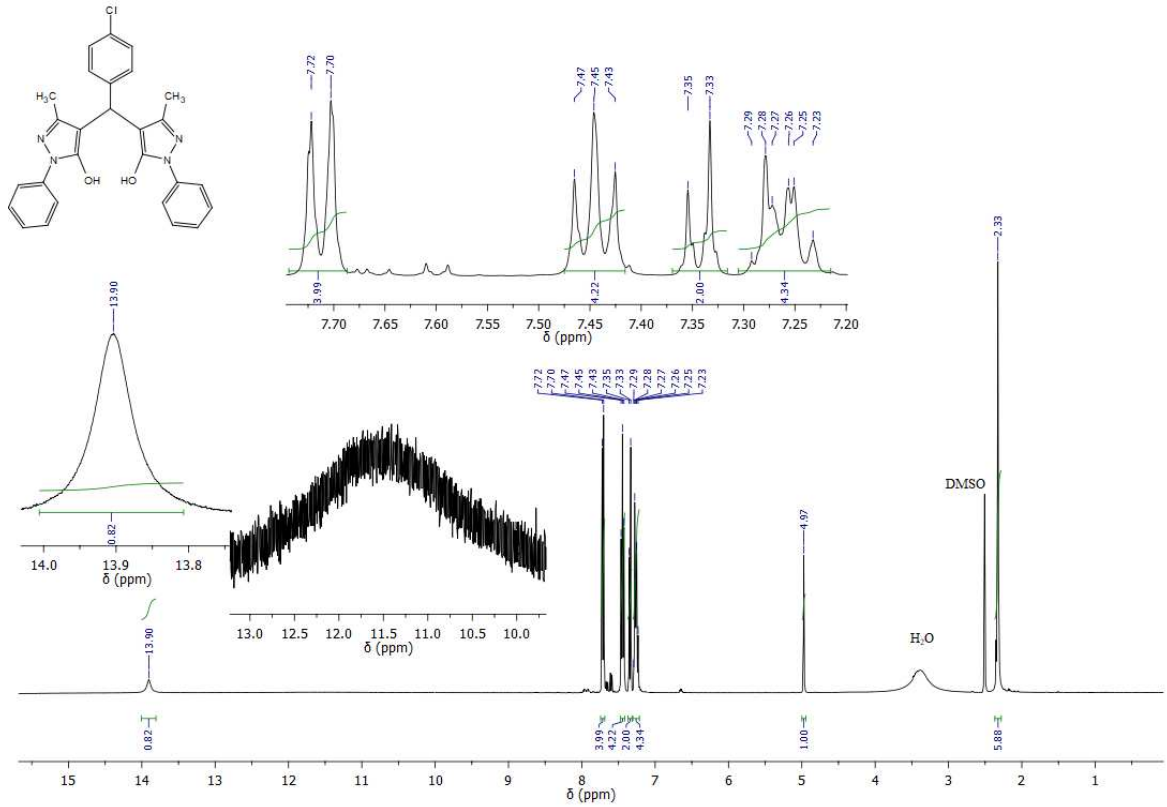


Figure 1. ^{1}H NMR spectra of 4,4′-(4-chlorophenylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ol) **14b**.

In the case of the derivative obtained from *p*-chlorobenzaldehyde, the authors included the result of a measurement of mass spectrum (ESI) of the sample, obtaining values for [M^{+}] 371 (100%), which corresponds to the structure of 4,9-dihydro-1-*H*-pyrazolo[3,4-*b*]quinoline **13a** (R = Cl). Elemental analysis also confirms this structure. However, the ^{1}H NMR spectrum indicates that in fact product **14b** was formed. Unfortunately, we do not know where this inaccuracy came from. Another problem occurs in the case of a product obtained from *p*-tolualdehyde **2a**. The ^{1}H NMR spectra is depicted in Figure 2.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 October 2023 doi:10.20944/preprints202310.0271.v1

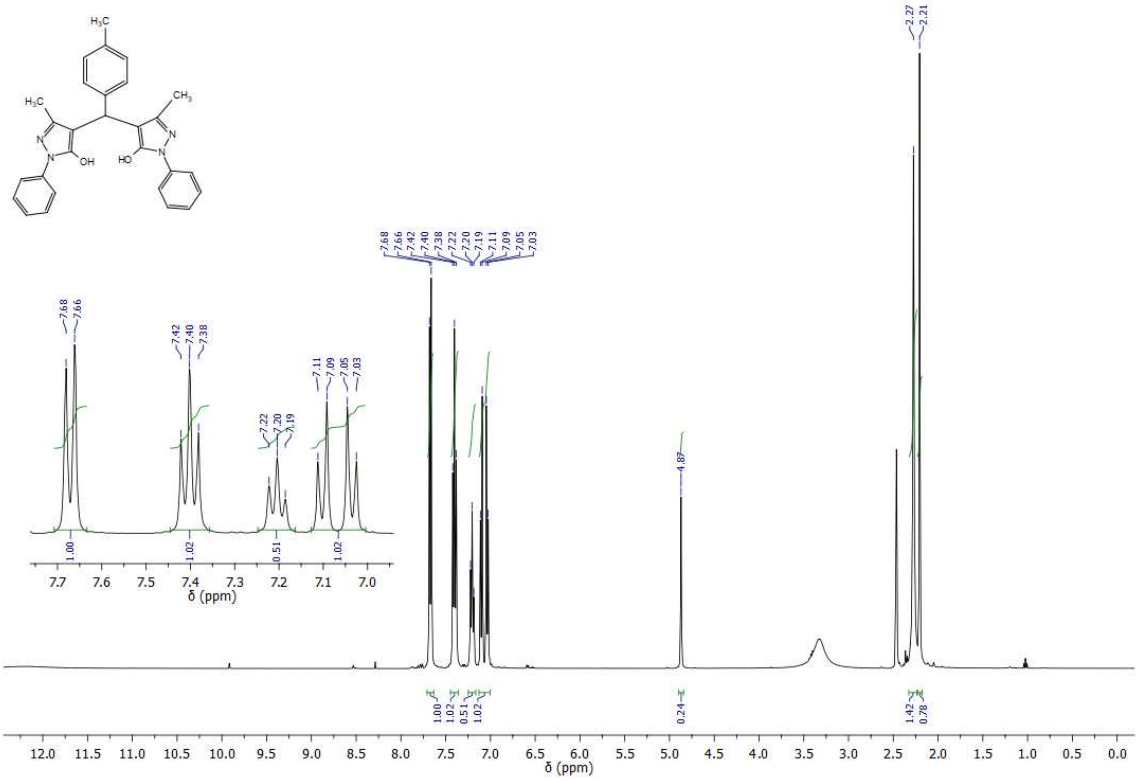


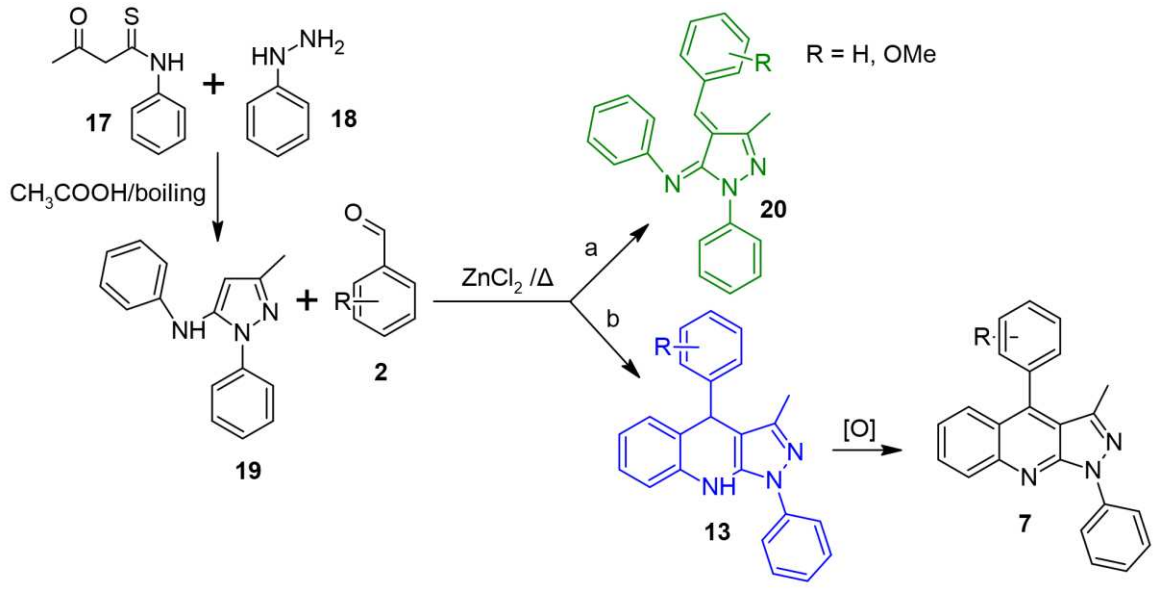
Figure 2. ^{1}H NMR spectra of 4,4′-(4-methylphenylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ol) **14a**.

In the case of the ^{1}H NMR spectrum of alleged 4-(*p*-methylphenyl)-4,9-dihydro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline **13a** (R = Me) the authors assigned each of the peaks located at 2.24 and 2.30 ppm respectively to three protons from methyl groups in each case. In fact, if we look closer at the ^{1}H NMR spectrum for **14a**, the ratio of the number of protons at 2.27 and 2.21 is 2:1. The same can be observed in publication of Mohammadi and Ghorbani-Choghamarani [29]. The spectra from publication of Hedge and Shetty are identical to those we obtained and the analysed compound cannot be 4-(*p*-methylphenyl)-1-phenyl-3-methyl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinoline **13a** though elemental analysis confirm the molecular structure.

Based on our results, we can conclude that the three-component reaction of aniline **5a**, aromatic aldehydes **2a-j**, 2-phenyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one **6b** and a catalytic amount of L-proline is completely useless when it comes to the synthesis of 4-aryl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinolines **13**. The question arises whether the previously mentioned structures **13** can be synthesized.

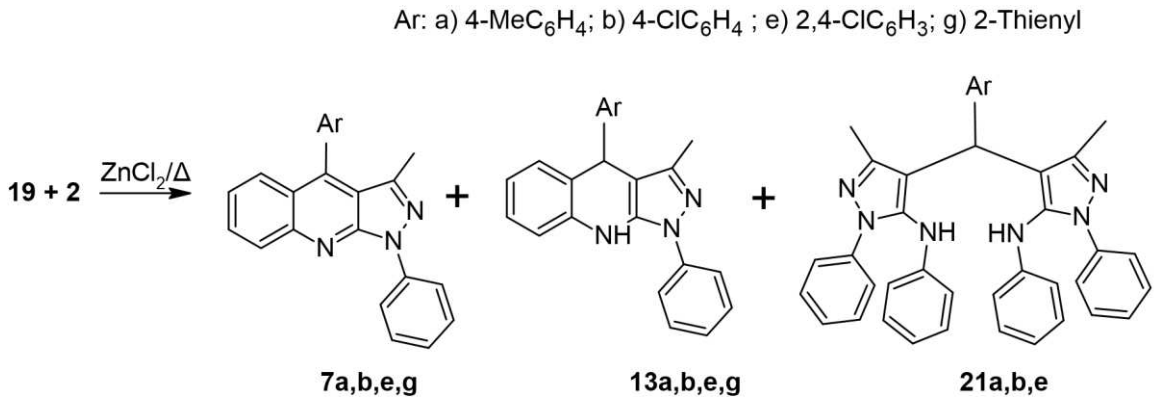
A different approach was used to check this. In 1911, Michaelis described the synthesis of 4-benzylidene-5-*N*-phenylaminopyrazoles **20** by reacting aromatic aldehydes **2** with 5-*N*-phenyl-3-methyl-1-phenylpyrazole **19** (Scheme 7) [30]. The author reported in the publication that he obtained two derivatives of this kind. However, later research by Tomasik *et al*. showed that the actual products formed in this reaction were 1*H*-pyrazolo[3,4-*b*]quinolines **7** [31].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 October 2023 doi:10.20944/preprints202310.0271.v1



Scheme 7. Cyclisation of 5-*N*-phenyl-3-methyl-1-phenylpyrazole to 4-aryl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinolines.

Michaelis and the authors of the later publication did not study the course of the reaction, but it can be expected that during it an intermediate products **13** can be formed and correspond to those described in the work of Hedge and Shetty. To test this hypothesis, the appropriate aminopyrazole **19** was synthesized from phenylhydrazine **18** and 3-oxo-*N*-phenylbutanethioamide **17**. In the next turn it was reacted with aldehydes **2a**, **2b**, **2e** and **2g** in the presence of anhydrous zinc chloride. Michaelis and Tomasik and their co-workers carried out a melting reaction of aromatic aldehyde **2** with 5-*N*-phenylpyrazole **19** in an open flask. The final yields of pyrazolo[3,4-*b*]quinoline **7** were in the order of 40-50%. Slightly larger when using a microwave field. If it is assumed that the intermediate product in this reaction is the 4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinoline **13** , it can be assumed that the oxygen present in the air plays a significant role in the oxidation of this compound. In order to eliminate its influence, the reaction was carried out in closed ampoules for 6 hours. After the end of heating and analysis of the post-reaction mixture by TLC, the presence of three products was found, namely 4-aryl-1*H*-pyrazolo[3,4-*b*]quinoline **7a,b,e,g,** 4-aryl-4,9-dihydro-1*H*-pyrazolo[3,4 -*b*]quinoline **13a,b,** and 4,4'-(arylmethylene)-bis-[3-methyl-*N*,1-diphenyl-1*H*-pyrazol-5-amine] **22** (Scheme 8).



Scheme 8. The final products from Michaelis protocol.

The yield of 1*H*-pyrazolo[3,4-*b*]quinoline was definitely lower (5-8%) than in the case of the reaction carried out under air condensation (as in the original work by Michaelis). Separation of the

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 October 2023 doi:10.20944/preprints202310.0271.v1

products was very troublesome due to the almost identical values R_f of starting **19** and resulted 4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinolines **13**. The products were separated by pre-removal of 1*H*-pyrazolo[3,4-*b*]quinoline with with residual unreacted aldehyde, and then the column was developed using a mixture of toluene and ethyl acetate in a ratio of 3:0.1 with a gradual increase in the amount of ethyl acetate to 3:0.4.

We performed the reaction only for four aldehydes **2a,b,e,g** because in the case of the other ones we were not able to separate final products **13** and **21** with a sufficient purity for analysis. In case of furfural **2j** as the only result we received a black tar. Figure 3 shows the ^{1}H NMR spectrum of 4-(4-methylphenyl)-1-phenyl-3-methyl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinoline **13a**. The signals presented in the spectrum do not coincide at all with those that are included in the supplementary materials of Shetty and Gatta. The proton at N-9 is visible at 6.32 ppm instead of 14.00 ppm. Both protons at 6.32 ppm and 5.28 ppm disappear after oxidation of **13a** when 1*H*-pyrazolo[3,4-*b*]quinoline **7a** is formed (Figure 4).

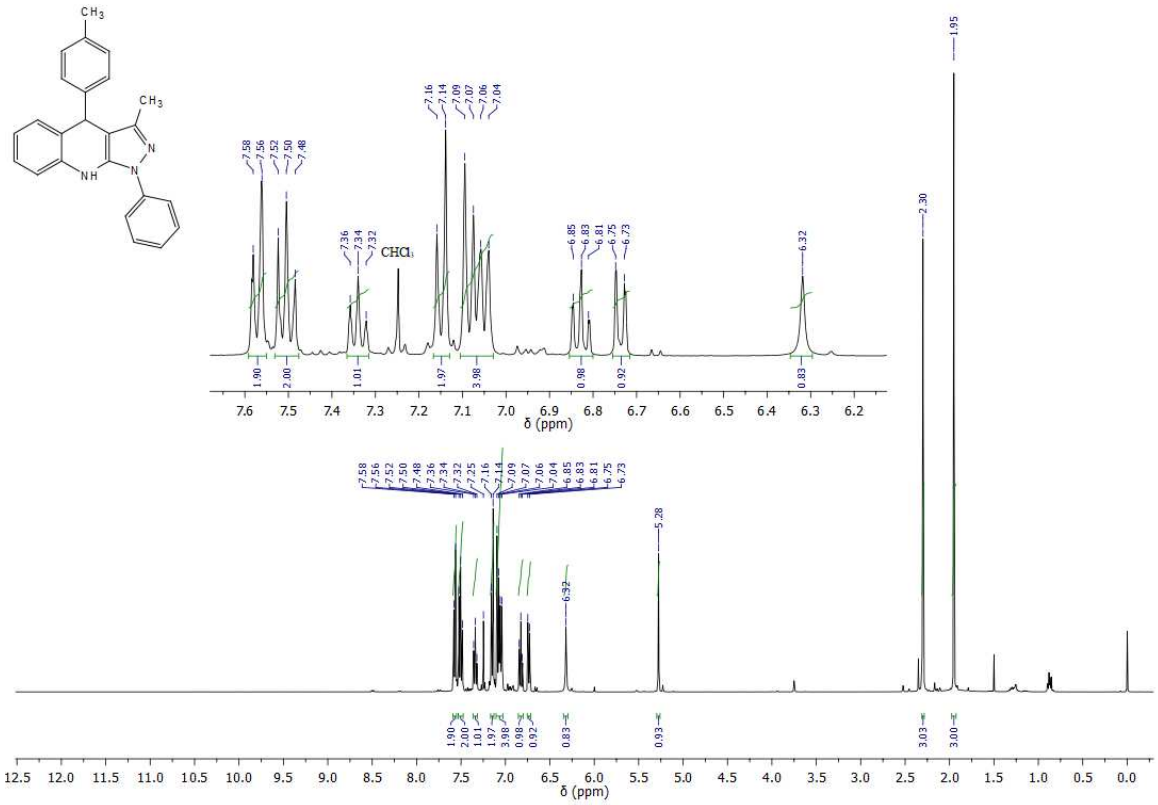


Figure 3. ^{1}H NMR spectra of 4-(4-methylphenyl)-4,9-dihydro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline **13a.**

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 October 2023 doi:10.20944/preprints202310.0271.v1

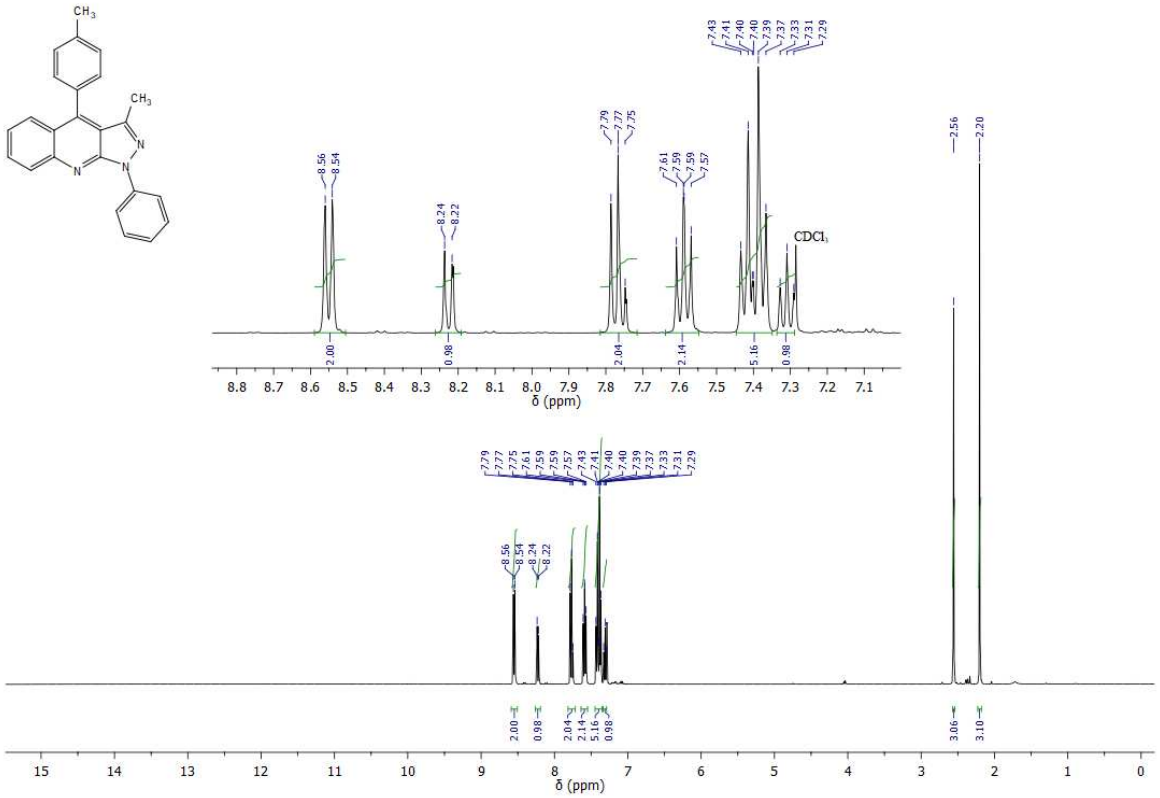


Figure 4. [1]H NMR spectrum of 4-(4-methylphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline **7a**.

After obtaining and establishing the structure, compounds **13a**, **13b, 13e** and **13g** were used as TLC standards when the three-component reaction was repeated with L-proline as a catalyst. These products were not found. The compounds **13** obtained by us can be transformed into fully aromatic pyrazolo[3,4-*b*]quinolines but obtaining them in pure form is pointless, because they themselves undergo oxidation during the reaction, forming systems **7**. Our goal was to synthesize them to check whether they are formed at all in the reaction we examined and establish the correct structure. Taking into account the experiments performed and the interpretation of the results, the issue of the synthesis of 4-aryl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinolines using a multi-component reaction remains a challenge.

3. Materials and Methods

3.1. Chemicals and Instruments

Chemicals and solvent were purchased from Aldrich/Merck and POCh (Polish chemical company) respectively. [1]H NMR and [13]C NMR spectra were recorded using Bruker Advance III (400 MHz) and Bruker Advance III (600 MHz) spectrometers (Jagiellonian University, Faculty of Chemistry). Elemental analysis was performed using the CHNS Vario MICRO Cube analyzer with electronic micro balance. Melting points were measured using a MEL-TEMP II cryometer (Agricultural University, Faculty of Food Chemistry). TLC chromatograms were visualized using a dual-band (254 and 365 nm) Spectroline UV lamp model ENF-260/FE. 70-230 mesh ASTM silica gel purchased from Merck KGaA was used as the stationary phase in the column chromatographic methods. 70-230 mesh ASTM (Activity Grade I) alumina was also purchased at Merck KGaA. Mass spectra were taken with a mass spectrometer coupled to a Shimadzu LCMS-8040 high performance liquid chromatograph (Jagiellonian University, Faculty of Chemistry).

3.2. Experimental Procedures

 doi:10.20944/preprints202310.0271.v1

3.2.1. An Attempt at the Synthesis of 4-Aryl-1-phenyl-3-methyl-4,9-dihydro-1H-pyrazolo[3,4-b]quinolines via Three Component Reaction According to Hegde and Shetty Protocol

Procedure a) 865 mg (5 mmol) of 2-phenyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one, 600 mg (5 mmol) *p*-tolualdehyde, 450 mg (5 mmol) mmol) aniline, 75 mg (20 mol%) L-proline and 10 cm^3 ethanol were introduced into a round bottom flask (25 cm^3) and placed in a heating block and boiled for 5 hrs under reflux condenser. After the end of heating, the reaction mixture was left for 24 hours in the refrigerator and the separated crystalline precipitate was filtered off. The filtrate was evaporated, the resulting oil was dissolved in chloroform and dried with anhydrous $MgSO_4$. The chloroform was evaporated and the oil obtained was dissolved in petroleum ether (40/60) and chromatographed on a silica gel column. The solution was evaporated and the light yellow oil was left in the refrigerator to solidify.

Procedure b): 5 mmoles of substrates without L-proline were used in the reaction.

4,4′-(4-Methylphenylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ol) **14a**

Procedure a: Colourless crystals, 820 mg, yield 72%, mp. 204-5 °C. Lit. 203-205 °C [32].

Procedure b: Colourless crystals, 880 mg, yield 78%, mp. 204-5 °C.

^{1}H NMR (400 MHz, DMSO-d_6,) δ, ppm (*J*, Hz): 7.67 (d, *J* = 7.7 Hz, 4H), 7.40 (t, *J* = 7.9 Hz, 4H), 7.20 (t, *J* = 7.3 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 4.87 (s, 1H); 2.27 (s, 6H), 2.21 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ, ppm: 146.8, 139.7, 135.3, 129.5, 129.2, 127.6, 126.1, 121.0, 33.3, 21.1, 12.1.

4-Methyl-*N*-[(1*E*)-phenylmethylidene]aniline **15a**

Pale yellow crystalline mass, 173 mg, yield 18%, mp. 40-42 °C. Lit. 40-41°C [24]. TLC testing (toluene:petroleum ether 40/60 ratio 1:1) showed the sample to have identical R_f values to the original Schiff base synthesized from aniline and *p*-tolualdehyde .

4,4′-(4-Chlorophenylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ol) **14b**

Procedure a: Colourless crystals, 878 mg, 74 %, mp. 205-6 °C. Lit. 206-8 °C [33]

Procedure b: Colourless crystals, 950 mg, 80 %, mp. 205-6 °C.

^{1}H NMR(400 MHz, $CDCl_3$) δ, ppm (*J*, Hz): 13.90 (s, 1H), 7.71 (d, *J* = 7.6 Hz, 4H), 7.45 (t, *J* = 8.0 Hz, 4H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.30 – 7.21 (m, 4H), 4.97 (s, 1H), 2.33 (s, 6H). ^{13}C NMR(100 MHz, $CDCl_3$) δ, ppm (*J*, Hz): 146.68, 141.63, 131.01, 129.59, 129.42, 129.38, 128.47, 121.02, 33.02, 12.06.

4,4′-(4-Fluorophenylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ol) **14c**

Procedure a: Colourless crystals, 900mg, 79%, mp. 168-9 °C. Lit. 180-1 °C [33].

Procedure b: Colourless crystals, 980 mg, 86%, mp. 167-8 °C.

^{1}H NMR (400 MHz, DMSO) δ, ppm (*J*, Hz): 13.95 (s, 1H), 7.72 (d, *J* = 7.7 Hz, 4H), 7.45 (t, *J* = 7.9 Hz, 4H), 7.31-7.23 (m, , 4H), 7.11 (t, *J* = 8.9 Hz, 4H), 4.97 (s, 1H), 2.33 (s, 6H).

4,4′-(4-Methoxyphenylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ol) **14d**

Procedure a: Colourless crystals, 230 mg (2 mmol scale), yield 49%, mp. 167-169°C. Lit. 165-167 °C [33].

^{1}HNMR (400 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 7.67 (d, *J* = 7,9 Hz, 4H), 7.40 (t, *J* = 7,6 Hz, 4H), 7.20 (t, *J* = 7,0 Hz, 2H), 7.12 (d, *J* = 8,3 Hz, 2H), 6.80 (d, *J* = 8,4 Hz, 2H), 4.86 (s, 1H), 4.86 (s, 3H), 2.27 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 158.04, 146.69, 134.45, 129.28, 128.70, 126.03, 121.03, 114.03, 55.52, 32.87, 11.73.

4,4′-(2,4-Dichlorophenylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ol) **14e**

Procedure a: Colourless crystals, 1100 mg, yield 86%, p. 234-5 °C. Lit. 228-230 °C [31]

Procedure b: Colourless crystals, 1000 mg, yield 79%, p. 233-5 °C.

^{1}H NMR(400 MHz, DMSO-d_6,) δ, ppm (*J*, Hz): 13.83 (s, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 4H), 7.55 (d, *J* = 2.2 Hz, 1H, 7.43 (dt, *J* = 8.9, 5.0 Hz, 5H 7.25 (t, *J* = 7.4 Hz, 2H), 5.10 (s, 1H), 2.29 (s, 6H). ^{13}C NMR(100 MHz, DMSO-d_6,) δ, ppm: 146.47, 138.93, 133.36, 132.12, 131.90, 129.39, 129.31, 127.45, 126.15, 121.07, 31.84, 12.28.

4,4′-(4-Nitrophenylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ol) **14f**

Procedure a: Colourless crystals, 850 mg, yield 71%, mp. 234-5 °C. Lit. 228-230 °C [31]

Procedure b: Colourless crystals, 900 mg, 75%, mp. 233-4 °C.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 October 2023 doi:10.20944/preprints202310.0271.v1

^{1}H NMR(400 MHz, DMSO-d$_6$,) δ, ppm (*J*, Hz): 13.87 (s, 1H), 8.18 (d, *J* = 8.9 Hz, 2H), 7.71 (d, *J* = 7.6 Hz, 4H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 4H), 7.26 (t, *J* = 7.4 Hz, 2H), 5.14 (s, 1H), 2.36 (s, 6H).^{13}C NMR(101 MHz, DMSO-d$_6$,) δ, ppm : 150.78, 146.75, 146.38, 129.40, 129.08, 126.20, 123.80, 121.07, 33.64, 12.05.

4,4′-(2-Thienylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ol) **14g**

Procedure a: Colourless crystals, 140 mg (2 mmol scale), 33%, mp. 187-189 °C. Lit. 189-190 °C [34].

Procedure b: Colourless crystals, 500mg (5 mmol scale), 45%, mp. 187-188 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$,) δ, ppm (*J*, Hz): 7.67 (d, *J* = 8,6 Hz, 1,0 Hz, 4H), 7,41 (t, *J* = 8.0 Hz, 4H), 7.27-7.18 (m, 3H), 6,87 (dd, *J* = 5.1 Hz, 3.5Hz, 1H), 6.73-6.69 (m, 1H), 5.09 (s, 1H), 2.28 (s, 6H). ^{13}C NMR (101MHz, DMSO-d$_6$) δ, ppm: 148.06, 146.34, 129.48, 127.30, 126.22, 124.69, 124.59, 29.98, 12.05.

4,4′-(4-Hydroxyphenylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ol) **14h**

The reaction was carried out on a 5 mmol scale using 30 ml of ethanol as a solvent.

Procedure a: Yellow crystals, 890 mg, yield 78%, mp. 158-160 °C. Lit. 153-155 °C [27].

Procedure b: Yellow crystals, 930 mg, yield 82%, mp. 158-159 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$,) δ, ppm (*J*, Hz): 13.94 (s, 1H), 9.18 (s, 1H), 7.72 (d, *J* = 7.8 Hz, 4H), 7.45 (t, *J* = 7.9 Hz, 4H), 7.25 (t, *J* = 7.3 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.68 (d, *J* = 8.6 Hz, 2H), 4.86 (s, 1H), 2.31 (s, 6H). ^{13}C NMR (101MHz, DMSO-d$_6$) δ, ppm: 155.96, 146.64, 132.73, 129.36, 128.55, 125.96, 120.95, 115.31, 32.84, 12.09.

4,4′-(3,4-Dimethoxyphenylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ol) **14i**

The reaction was carried out on a 5 mmol scale using 30 ml of ethanol as a solvent.

Procedure a: Colourless crystals, 1050 mg, 85%, mp. 208-9 °C. Lit. 194-196 °C [27].

Procedure b: Colourless crystals, 1100 mg, 89%, mp. 207-9 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$,) δ, ppm (*J*, Hz): 14.02 (s, 1H), 12.39 (s, 1H), 7.71 (d, *J* = 7.7 Hz, 4H), 7.45 (t, *J* = 7.9 Hz, 4H), 7.25 (t, *J* = 7.3 Hz, 2H), 6.85 (ddd, *J* = 17.9, 8.6, 1.6 Hz, 3H), 4.89 (s, 1H), 3.71 (s, 1H), 3.66 (s, 1H), 2.32 (s, 6H). ^{13}C NMR (101MHz, DMSO-d$_6$) δ, ppm: 148.86, 147.70, 146.63, 135.42, 129.38, 121.05, 119.76, 112.23, 112.09, 56.02, 55.96, 33.38, 12.13.

4,4′-(2-Furylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ol) **14j**

The compound could not be isolated from the post-reaction mixture, but its presence was detected using TLC and compared with the original substance obtained in the reaction of pyrazolone **6b** and 2-furylaldehyde.

(4*E*)-4-[(4-hydroxyphenyl)methylidene]-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **16a**

Procedure a: Orange crystals, 970 mg, yield 69%, mp. 239-240 °C. Lit. 238 °C [35]

^{1}H NMR (600 MHz, DMSO) δ, ppm (*J*, Hz): 10.84 (s, 1H), 8.64 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 7.6 Hz, 2H), 7.70 (s, 1H), 7.45 – 7.40 (m, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 8.9 Hz, 2H), 2.32 (s, 3H).

(4*E*)-4-[(3,4-dimethoxyphenyl)methylidene]-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **16b**

Procedure a: Orange crystals, 1230 mg, yield 76%, mp. 165-6 °C.

^{1}H NMR (600 MHz, CDCl$_3$) δ, ppm (*J*, Hz): 9.02 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 2H), 7.71 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.45 – 7.41 (m, 2H), 7.32 (s, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 4.06 (s, 3H), 3.99 (s, 3H), 2.35 (s, 3H).

Calcd for: $C_{19}H_{18}N_2O_3$ C 70.79; H 5.63; N 8.69 Found 70.63; H 5.46; N 8.48.

3.2.2. A Synthesis of Selected 4,4′-(4-Arylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-oles) from Aldehydes 2 and 5-Methyl-2-phenyl-2,4-dihydro-3H-pyrazole-3-one 6b - General Procedure

4,4′-(4-Methylphenylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ol) **14a**

A round-bottomed flask (50 mL) equipped with reflux condenser and magnetic stirring bar was charged with *p*-tolualdehyde (120 mg, 1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazole -3-one (340 mg, 2 mmol) and ethanol (10 mL). The content was boiled for 5 hours. After a few minutes formation of light pink precipitate was observed. After cooling the precipitate was filtered off and crystallized from ethanol/DMF mixture.

Pale pink crystals, 350 mg, 77%, mp. 204-5 °C.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 October 2023 doi:10.20944/preprints202310.0271.v1

4,4′-(4-Hydroxyphenylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ol) **14h**

After cooling the solution was evaporated and the resulted solid was crystallized from methanol. Light yellow crystals, 375 mg, 82%, mp. 158-160 °C. Lit. 153-155 °C [27].

4,4′-(3,4-Dimethoxyphenylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ol) **14i**

Pale yellow crystals, 425 mg, 85%, mp. 208-9 °C.

4,4′-(2-Furylmethylene)-bis-(3-methyl-1-phenylpyrazol-5-ol) **14j**

Colourless crystals, 278mg, 65%, mp. 187-189 °C. Lit. 188-189 °C [26].

^{1}H NMR (400 MHz, DMSO-d_6,) δ, ppm (*J*, Hz): 13.85 (s, 1H), 7.72 (d, *J* = 7.7 Hz, 4H), 7.51 (s, 1H), 7.45 (t, *J* = 7.9 Hz, 4H), 7.26 (t, *J* = 7.4 Hz, 2H), 6.35 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.13 (d, *J* = 3.2 Hz, 1H), 4.99 (s, 1H), 2.31 (s, 6H).^{13}C NMR (101MHz, DMSO-d_6) δ, ppm: 154.59, 146.42, 142.01, 129.38, 126.06, 121.02, 110.83, 106.60, 28.73, 11.96.

3.2.3. Synthesis of 4-Aryl-4,9H-dihydro-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]quinolines by Cyclisation of 3-Methyl-N,1-diphenyl-1H-pyrazol-5-amine 20 with Aldehydes 2

3-Oxo-*N*-phenylbutanethioamide **18**

The compound was prepared according to literature procedure [36].

3-Methyl-*N*,1-diphenyl-1*H*-pyrazol-5-amine **20**

In a round bottom flask (100 cm^3) were placed 6.7 g (0.035 mol) of 3-oxo-*N*-phenylbutanethiamide, 4 g (0.037 mol) of phenylhydrazine and 20 cm^3 of glacial acetic acid. The mixture was refluxed for 12 hours until the evolution of hydrogen sulfide ceased. The acetic acid was evaporated and the resulting oil was treated with 10% $NaHCO_3$. The mixture was extracted with methylene chloride. The organic layer was dried with anhydrous $MgSO_4$. After removal of the sulfate, the solution was passed through a layer of alumina, evaporated and crystallized from toluene and petroleum ether with small amount of charcoal to decolorize final product. 6.74 g (77%) of light yellow crystals were obtained. M.p. 119-120 °C. Lit. 120 °C, 122-3 °C [37,38].

A glass vial (10 mL) equipped with magnetic stirring bar was charged with anhydrous zinc chloride (200mg, 1.5 mmol), *p*-tolualdehyde **2a** (180mg, 1.5 mmol) and **20** (380 mg, 1.5 mmol). The vial was closed with with an air condenser and inserted into aluminum heating block and heated at 125 °C for 6 hours with stirring. After cooling the melt was digested with ethanol, sonicated and filtered of to remove pyrazolo[3,4-*b*]quinoline **7a**. A filtrate was evaporated and the resulted oil was dissolved in toluene and chromatographed on column packed with silica gel (Merck 60, 70-230 mesh) using toluene – ethyl acetate mixture as eluent (toluene: AcOEt/ 3:0.1 →3:0.4) to separate **13a** from **22a**. The experiment was performed in two-fold way – in an open vial and with a closed vial.

4-(4-Methylphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline **7a**

Yellow crystals, 150 mg, 26.7% (an open vial), 35 mg, 6.3% (a closed vial), mp. 208-210 °C. Lit. 206-207°C [11].

^{1}H NMR(400 MHz, $CDCl_3$) δ, ppm (*J*, Hz): 8.55 (d, *J* = 7.7 Hz, 2H), 8.23 (d, *J* = 8.1 Hz, 1H), 7.77 (t, *J* = 7.7 Hz, 4H), 7.59 (dd, *J* = 8.4, 7.6 Hz, 4H), 7.40 (dt, *J* = 13.7, 8.1 Hz, 5H), 7.31 (t, *J* = 7.4 Hz, 1H), 2.56 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ, ppm: δ 150.18, 148.49, 144.76, 143.97, 140.02, 138.62, 131.93, 130.25, 129.64, 129.03, 128.94, 127.06, 124.88, 123.81, 120.33, 116.46, 21.46, 15.07.

4-(4-Methylphenyl)-4,9-dihydro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline **13a**

Colourless crystals, 67 mg, 11.6 % (open vial), 174 mg, 30,1% (closed vial), m.p. 178-180 °C.

^{1}H NMR(400 MHz, $CDCl_3$) δ, ppm (*J*, Hz): 7.60-7.54(m, 2H); 7.54-7.47(m, 2H); 7.34(t, *J* = 7.3 MHz, 1H), 7,15(d, *J* = 8.1Hz, 2H); 6.86-6.79(m, 1H); 6.74(dd, *J* = 8.4; 0.9Hz, 1H); 6.29 (s, 1H, N-H), 5.29(s, 1H), 2.31(s, 3H); 1.95(s, 3H). ^{13}C NMR(100 MHz, $CDCl_3$) δ, ppm : 147.72; 144.35; 138.58; 138.55, 137.20; 135.95; 131.32; 129.90, 129.33; 128.23; 127.25; 126.98; 125.00; 122.79; 122.13; 115.90; 100.77; 42.06, 21.15, 12.66.

Calculated for $C_{24}H_{21}N_3$ ESI (M + H$^+$) = 352,1808. Measured: ESI(M+H$^+$) = 352,20.

4,4′-(4-Metylphenylmethylene)-bis-[3-methyl-*N*,1-diphenyl-1*H*-pyrazol-5-amine] **22a**

Colourless crystals, 218 mg (closed vial), 45 %, mp. 198-99 °C

^{1}H NMR(400 MHz, $CDCl_3$) δ, ppm (*J*, Hz): 7,45(d, *J* = 7.9Hz, 4H); 7.30-7.21(m, 5H); 7.16(t, *J* = 7.4Hz, 2H); 7.03-6.82(m, 7H); 6.66(t, *J* = 7.3Hz, 2H); 6.26(d, *J* = 7.8Hz, 4H); 5.18(s, 1H); 4.58(s, 2H),

2,24(s, 3H); 1,97(s, 6H). ^{13}C NMR(101 MHz, $CDCl_3$) δ, ppm: 148.33; 144.71; 139.07; 137.37; 136.09; 129.09; 128.89; 128.18; 126.68; 122.92; 119.62; 115.07; 113.91; 36.34 (C**H-**methylene); 21.06 ($C_6H_4C\mathbf{H_3}$); 13.94 (3-CH_3).

Cald. for $C_{40}H_{36}N_6$: **ESI** ($M+H^+$) = 601,3074. Measured : **ESI** ($M+H^+$) = 601,35.

4-(*p*-Chlorophenyl)-1-phenyl-3-methyl-1*H*-pyrazolo[3,4-*b*]quinoline **7b**

Yellow crystals, 32 mg, 5.4%, mp. 230-231°C. The sample was identified with original one prepared according to literature procedure [39].

4-(*p*-Chlorophenyl)-4,9-dihydro-1-phenyl-3-methyl-1*H*-pyrazolo[3,4-*b*]quinoline **13b**

Pale yellow powder, 53 mg, 8.9%, m.p. 129-130 °C.

^{1}H NMR(400 MHz, $CDCl_3$) δ, ppm (*J*, Hz): 7.62-7.57(m, 2H); 7.57-7.49(m, 2H); 7.41-7.34(m, 1H); 7.32-7.26(m, 1H); 7.26-7.20(m, 1H); 7.15-7.07(m, 1H); 7.03(t, *J* = 7.5Hz, 1H); 6.91-6.83(m, 1H); 6.78(dd, *J* = 8.0Hz; 0.8Hz, 1H), 6.41(s, 1H, N-H); 5,34(s, 1H, C-H); 1,98(s, 3H, 3-CH_3). ^{13}C NMR(100 MHz, $CDCl_3$) δ, ppm:147.42; 145.72; 138.52; 137.10; 132.16; 131.14; 129.82; 129.52; 128.48; 127.40; 126.98; 124.15; 122.69; 122.08, 115.89; 100.05; 41.11; 12.59.

Calcd for $C_{23}H_{18}ClN_3$ C 74.29; H 4.88; N 11.30. Found C 74.03; H 4.56; N 11.18.

4,4'-(4-Chlorophenylmethylene)-bis-[3-methyl-*N*,1-diphenyl-1*H*-pyrazol-5-amine)] **22b**

White powder, 222 mg, 44.5%, mp. 202-3 °C.

^{1}H NMR(400 MHz, $CDCl_3$) δ, ppm: 7.51-7.43(m, 4H); 7.31(t, *J* = 7.8Hz, 4H); 7.21(t, *J* = 7.4Hz, 2H); 7.10(d, *J* = 8.5Hz, 2H); 7.02(dd, *J* = 16.5Hz, 8.7Hz, 6H); 6,72(t, *J* = 7.4Hz, 2H); 6,29(d, *J* = 7.7Hz, 4H); 5,20(s, 1H); 4,59(s, 2H); 2,02(s, 6H). ^{13}C NMR(100 MHz, $CDCl_3$) δ, ppm :148.00; 144.58; 139.04; 138.83; 137.26; 132.21; 129.37; 129.07; 129.01; 128.55; 126.78; 122.92; 119.69; 114.66; 113.74; 36.21; 13.91.

Calcd for $C_{39}H_{33}ClN_6$ C 75.41; H 5.35; N 13.53 Found C 75.32; H 5.23; N 13.48.

4-(2,4-Dichlorophenyl)-1-phenyl-3-methyl-1*H*-pyrazolo[3,4-*b*]quinoline **7e**

In this procedure 300 mg of **20** and 210 mg of 2,4-dichlorobenzaldehyde were used for reaction.

Yellow crystals, 24 mg (closed vial), 4,9 %, m.p. 158-9 °C.

^{1}H NMR(400 MHz, $CDCl_3$) δ, ppm (*J*, Hz): 8,54(dd, *J* = 8.7; 1,1Hz, 2H); 8.26(d, *J* = 8.3Hz, 1H); 7.83-7.77(m, 1H); 7.72(d, *J* = 2.0 Hz, 1H); 7.62-7.50(m, 2H); 7.46-7.40(m, 1H), 7.38(d, *J* = 8.2Hz, 1H); 7.35-7.29(m, 1H); 2.22(s, 3H, 3-Me).^{13}C NMR(100 MHz, $CDCl_3$) δ, ppm: 150.13; 148.53; 143.17; 139.85; 139.55; 135.85; 134.73; 132.69; 132.14; 130.45; 129.73; 129.28; 129.06; 127.24; 126.00; 125.09; 124.55; 122.92; 120.33; 116.31; 14.17.

Calcd for $C_{23}H_{15}Cl_2N_3$ C 68,33; H 3.74; N 10.39. Found C 68.14; H 3.45; N 10.28.

4-(*p*-2,4-Dichlorophenyl)-4,9-dihydro-1-phenyl-3-methyl-1*H*-pyrazolo[3,4-*b*]quinoline **13e**

Pale yellow crystals, 128 mg, 27%, m.p. 220-1°C.

^{1}H NMR(400 MHz, $CDCl_3$) δ, ppm: 7.62-7.57(m, 2H); 7.54(dd, *J* = 10.5Hz, 5.2Hz, 2H); 7,44(t, *J* = 1.1Hz, 1H); 7.41-7.35(m, 1H); 7.16(d, *J* = 1.1Hz, 2H); 7.14-7.09 (m, 1H); 7.08(d, *J* = 7.7Hz, 1H); 6.90-6.84(m, 1H); 6.78(dd, *J* = 8.0Hz, 0.8Hz, 1H); 6.42(s, 1H, N-H); 5.99(s, 1H, C-H); 1.97(s, 3H). ^{13}C NMR(100 MHz, $CDCl_3$) δ, ppm: 147.37; 143.43; 138.76; 138.42; 137.10; 132.76; 132.52; 132.43; 130.74; 129.83; 128.88; 128.11; 127.66; 127.03; 123.65; 122.48; 122.24; 115.90; 99.69; 36.85; 11.91.

Calcd for $C_{23}H_{17}Cl_2N_3$ C 67,99; H 4,22; N 10,34. C 67.81; H 4.08; N 10.17.

4-(Thienyl-2-ylo)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline **7d**

Yellow crystals, 95 mg (closed vial), 17%, m.p. 141-2 °C.

^{1}H NMR(400 MHz, $CDCl_3$) δ, ppm (*J*, Hz): 8,48(dd, *J* = 8.7Hz, 1.1Hz, 2H); 8.17(d, *J* = 7.8Hz, 1H); 7,89(d, *J* = 8.6Hz, 1H); 7.77-7.71(m, 1H); 7.64(dd, *J* = 5.1Hz, 1.2Hz, 1H); 7.58-7.51(m, 2H); 7.43-7.38(m, 1H); 7.31-7.23(m, 3H), 2,3(s, 3H). ^{13}C NMR(101 MHz, $CDCl_3$) δ, ppm: 153.47; 146.80; 139.27; 139.17; 138.29; 130.89; 129.93; 127.76; 126.99; 126.82; 125.33; 124.10; 123.65; 123.06; 121.50; 117.28; 99.95; 36.85; 1267.

Calcd for: $C_{21}H_{15}N_3S$ C 73.87; H 4.43; N 12.31. Found C 73.57; H 4.28; N 12.18.

4-(Thienyl-2-ylo)-4,9-dihydro-3-methyl-1-phenyl-1*H*-pirazolo[3,4-*b*]quinoline **13g**

Colourless crystals, 150 mg, 29 %, m.p. 274-6 °C.

^{1}H NMR(400 MHz, $CDCl_3$) δ, ppm: 9.02(s, 1H); 7.58-7.46(m, 4H); 7.32(t, *J* = 7.2Hz, 1H); 7.26(t, *J* = 7.5 Hz, 1H); 7.12(d, *J* = 7.6Hz, 1H); 7.04(d, *J* = 4.1Hz, 2H); 6.98(d, *J* = 4.1Hz, 1H); 6,88(dd, *J* = 5.0Hz, 3.5Hz, 1H); 6.83-6.75(m, 1H); 5.67(s, 1H); 1.90(s, 3H). ^{13}C NMR(100 MHz, $CDCl_3$) δ, ppm: 153.47;

146.80; 139.27; 139.17; 138.29; 130.89; 129.93; 127.76; 126.99; 126.82; 125.42; 124.10; 123.65; 123.06; 121.50; 117.28; 99.95; 36.85; 12.67.

Calculated for $C_{21}H_{15}N_3S$: ESI(M+H$^+$) = 344,1216. Measured: ESI(M+H$^+$) = 344,10.

4. Conclusions

Multicomponent reactions are an extremely valuable tool in organic synthesis. For this reason, we were interested in a three-component reaction in which 4-aryl-4,9-dihydro-1*H*-pyrazolo[3,4-*b*]quinolines can be prepared readily available commercial components like aniline, aromatic aldehydes, 2-phenyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one and a catalytic amount of L-proline. These compounds can be oxidized at a later stage to obtain fully aromatic systems. Unfortunately, we were unable to repeat the results described in the publication and obtain the expected systems so we cannot agree with the authors' statement "*In conclusion, a simple and efficient protocol for one-pot multicomponent synthesis of 1H-pyrazolo[3,4-b]quinolines using L-proline as a catalyst has been developmed*" [18]. These ones have been prepared by a different method and compared with the samples obtained according to original protocol. It seems to us that the authors simply misinterpreted the data they obtained.

Supplementary Materials: The ^{1}H NMR and ^{13}C NMR data of investigated compounds are available online.

Author Contributions: A.D. writing-original draft preparation and final corretions; AD/MK-design the study, organic synthesis, data analysis; AG, T.U. Spectra analysis; E.P., K.M., O.H. – organic synthesis, sample preparations. All authors have read and agreed to the published version of the manuscript.

Funding: there was no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Willstätter, R. III. Synthese des Tropans und Tropidins. *Ann. Chem. Pharm.* **1901**, *317*, 307–374, doi:10.1002/jlac.19013170303.
2. Investigating a scientific legend: the tropinone synthesis of Sir Robert Robinson, F. R. S. *Notes Rec. R. Soc. Lond.* **1993**, *47*, 277–296, doi:10.1098/rsnr.1993.0034.
3. Strecker, A. Ueber einen neuen aus Aldehyd - Ammoniak und Blausäure entstehenden Körper. *Ann. Chem. Pharm.* **1854**, *91*, 349–351, doi:10.1002/jlac.18540910309.
4. Mannich, C.; Krösche, W. Ueber ein Kondensationsprodukt aus Formaldehyd, Ammoniak und Antipyrin. *Arch. Pharm. Pharm. Med. Chem.* **1912**, *250*, 647–667, doi:10.1002/ardp.19122500151.
5. Jiang, B.; Rajale, T.; Wever, W.; Tu, S.-J.; Li, G. Multicomponent reactions for the synthesis of heterocycles. *Chem. Asian J.* **2010**, *5*, 2318–2335, doi:10.1002/asia.201000310.
6. Graebin, C.S.; Ribeiro, F.V.; Rogério, K.R.; Kümmerle, A.E. Multicomponent Reactions for the Synthesis of Bioactive Compounds: A Review. *Curr. Org. Synth.* **2019**, *16*, 855–899, doi:10.2174/1570179416666190718153703.
7. Insuasty, D.; Castillo, J.; Becerra, D.; Rojas, H.; Abonia, R. Synthesis of Biologically Active Molecules through Multicomponent Reactions. *Molecules* **2020**, *25*, doi:10.3390/molecules25030505.
8. Zhi, S.; Ma, X.; Zhang, W. Consecutive multicomponent reactions for the synthesis of complex molecules. *Org. Biomol. Chem.* **2019**, *17*, 7632–7650, doi:10.1039/C9OB00772E.
9. Danel, A.; Gondek, E.; Kucharek, M.; Szlachcic, P.; Gut, A. 1H-Pyrazolo3,4-bquinolines: Synthesis and Properties over 100 Years of Research. *Molecules* **2022**, *27*, doi:10.3390/molecules27092775.
10. Quiroga, J.; Insuasty, B.; Hormaza, A.; Saitz, C.; Jullian, C. Synthesis of 4-aryl-4,7,8,9-tetrahydro-6H-pyrazolo[3,4- b]quinolin-5-ones. *Journal of Heterocyclic Chemistry* **1998**, *35*, 575–578, doi:10.1002/jhet.5570350313.
11. Chaczatrian, K.; Chaczatrian, G.; Danel, A.; Tomasik, P. A Facile Synthesis of 4-Aryl-1H-pyrazolo[3,4-b]quinolines. *ChemInform* **2004**, *35*, doi:10.1002/chin.200402163.
12. Ren, Y.-M.; Jin, S.; Yan, H.-J.; Zhang, Z. PEG1000-Based Dicationic Acidic Ionic Liquid Catalyzed One-Pot Synthesis of 4-Aryl-3-Methyl-1-Phenyl-1H-Benzo[h]pyrazolo [3,4-b]quinoline-5,10-Diones via Multicomponent Reactions. *Catalysts* **2015**, *5*, 1649–1656, doi:10.3390/catal5041649.

13. Wu, L.-Q.; Dong, R.-Y.; Yang, C.-G.; Yan, F.-L. Synthesis of 4-Aryl-3-Methyl-1-Phenyl-1 H -Benzo[h]Pyrazolo[3,4- b]Quinoline-5,10-diones Using Diammonium Hydrogen Phosphate as an Efficient and Versatile Catalyst in Water. *Jnl Chinese Chemical Soc* **2010**, *57*, 19–23, doi:10.1002/jccs.201000003.
14. Vachan, B.S.; Karuppasamy, M.; Vinoth, P.; Vivek Kumar, S.; Perumal, S.; Sridharan, V.; Menéndez, J.C. Proline and its Derivatives as Organocatalysts for Multi- Component Reactions in Aqueous Media: Synergic Pathways to the Green Synthesis of Heterocycles. *Adv. Synth. Catal.* **2020**, *362*, 87–110, doi:10.1002/adsc.201900558.
15. Patel, A.J.; Patel, V.C.; Dholakia, A.B.; Patel, D.S. L-Proline Catalyzed Synthesis of Heterocycles: A Review. *Organic Preparations and Procedures International* **2023**, 1–27, doi:10.1080/00304948.2023.2200357.
16. Gadkari, Y.U.; Shanbhag, R.D.; Telvekar, V.N. An Efficient One-Pot, Multicomponent Synthesis of 1, 3-Thiazolidin-4- Ones Using L-Proline as Catalyst in Water. *LOC* **2022**, *19*, 9–13, doi:10.2174/1570178618666210119121734.
17. Karamthulla, S.; Pal, S.; Parvin, T.; Choudhury, L.H. L-proline catalyzed multicomponent reactions: facile access to 2H-benzo[g]pyrazolo[3,4-b]quinoline-5,10(4H,11H)-dione derivatives. *RSC Adv* **2014**, *4*, 15319–15324, doi:10.1039/C4RA00876F.
18. Hegde, H.; Shetty, N.S. Facile one-pot multicomponent synthesis of 1H-pyrazolo[3,4-b]quinolines using L-proline as a catalyst. *Chem Heterocycl Comp* **2017**, *53*, 883–886, doi:10.1007/s10593-017-2152-3.
19. Casadia, I.; Albuquerque, D.Y. de; Carmo Capiotto, A.d.; Pereira de Pereira, C.M.; Pizzuti, L. Oxidative Aromatization of Pyrazolines. *Curr. Org. Synth.* **2017**, *14*, doi:10.2174/1570179414666161230151123.
20. Jenkins, R.N.; Hinnant, G.M.; Bean, A.C.; Stephens, C.E. Aerobic aromatization of 1,3,5-triarylpyrazolines in open air and without catalyst. *Arkivoc* **2015**, *2015*, 347–353, doi:10.3998/ark.5550190.p009.458.
21. Nakamichi, N.; Kawashita, Y.; Hayashi, M. Oxidative aromatization of 1,3,5-trisubstituted pyrazolines and Hantzsch 1,4-dihydropyridines by Pd/C in acetic acid. *Org. Lett.* **2002**, *4*, 3955–3957, doi:10.1021/ol0268135.
22. Rurack, K.; Danel, A.; Rotkiewicz, K.; Grabka, D.; Spieles, M.; Rettig, W. 1,3-Diphenyl-1H-pyrazolo3,4-bquinoline: a versatile fluorophore for the design of brightly emissive molecular sensors. *Org. Lett.* **2002**, *4*, 4647–4650, doi:10.1021/ol027025i.
23. Tomasik, D.; Tomasik, P.; Abramovitch, R.A. Friedländer condensation of 1 H -pyrazolin-5-ones with O -aminobenzaldehydes. Synthesis of 1 H -pyrazolo[3,4- B]quinolines. *Journal of Heterocyclic Chemistry* **1983**, *20*, 1539–1543, doi:10.1002/jhet.5570200620.
24. Song, Q.-W.; Yu, B.; Liu, A.-H.; He, Y.; Yang, Z.-Z.; Diao, Z.-F.; Song, Q.-C.; Li, X.-D.; He, L.-N. PEG400-enhanced synthesis of gem-dichloroaziridines and gem-dichlorocyclopropanes via in situ generated dichlorocarbene. *RSC Adv.* **2013**, *3*, 19009, doi:10.1039/c3ra43307b.
25. Hennig, L.; Alva-Astudillo, M.; Mann, G.; Kappe, T. New aspects in the reaction of azomethines with cyclic CH-acidic compounds. *Monatsh Chem* **1992**, *123*, 571–579, doi:10.1007/BF00816851.
26. Phatangare, K.R.; Padalkar, V.S.; Gupta, V.D.; Patil, V.S.; Umape, P.G.; Sekar, N. Phosphomolybdic Acid: An Efficient and Recyclable Solid Acid Catalyst for the Synthesis of 4,4′-(Arylmethylene)bis(1H-pyrazol-5-ols). *Synthetic Communications* **2012**, *42*, 1349–1358, doi:10.1080/00397911.2010.539759.
27. Keshavarz, M.; Vafaei-Nezhad, M. Design and Characterization of l-Prolinate-Amberlite as a Novel Heterogeneous Organocatalyst and Its Catalytic Application in the Synthesis of Pyrazol-Derivates. *Catal Lett* **2016**, *146*, 353–363, doi:10.1007/s10562-015-1668-3.
28. Tamoradi, T.; Mousavi, S.M.; Mohammadi, M. Synthesis of a new Ni complex supported on CoFe 2 O 4 and its application as an efficient and green catalyst for the synthesis of bis(pyrazolyl)methane and polyhydroquinoline derivatives. *New J. Chem.* **2020**, *44*, 8289–8302, doi:10.1039/D0NJ00223B.
29. Mohammadi, M.; Ghorbani-Choghamarani, A. Hercynite silica sulfuric acid: a novel inorganic sulfurous solid acid catalyst for one-pot cascade organic transformations. *RSC Adv* **2022**, *12*, 26023–26041, doi:10.1039/d2ra03481f.
30. Michaelis, A. Über 5-Aminopyrazole und über Iminopyrine. I. Über substituierte 5-Iminopyrazolone und über 5-Aminopyrazole. *Ann. Chem. Pharm.* **1911**, *385*, 1–43, doi:10.1002/jlac.19113850102.
31. Danel, A.; Chaczatrian, K.; Tomasik, P. Microwave-assisted, facile route to 1H-pyrazolo[3,4-b]quinolines. *Arkivoc* **2000**, *2000*, 51–57, doi:10.3998/ark.5550190.0001.108.
32. Eskandari, K.; Karami, B.; Khodabakhshi, S. An Unexpected Catalytic Synthesis of Novel and Known Bis(Pyrazolyl) Methanes by the use of α -aryl- N -phenyl Nitrones in Aqueous Media. *Journal of Chemical Research* **2014**, *38*, 600–603, doi:10.3184/174751914X14114871789226.
33. Keshavarz, M.; Zarei Ahmady, A.; Vaccaro, L.; Kardani, M. Non-Covalent Supported of l-Proline on Graphene Oxide/Fe_3O_4 Nanocomposite: A Novel, Highly Efficient and Superparamagnetically Separable Catalyst for the Synthesis of Bis-Pyrazole Derivatives. *Molecules* **2018**, *23*, doi:10.3390/molecules23020330.
34. Gouda, M.A.; Al-Balawi, M.M.M.; Abu-Hashem, A.A. One-pot pseudo five-component synthesis and antioxidant evaluation of 4,4'-(aryl-methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol). *Eur. J. Chem.* **2016**, *7*, 363–367, doi:10.5155/eurjchem.7.3.363-367.1474.

35. Thummar, B.B.; Tarpada, U.P.; Raval, D.K. Study on One-pot Biginelli-like Synthesis of Pyrazolo[3,4- d]pyrimidines in Bronsted Acidic Ionic Liquid Under Sonication and its Mechanism. *Journal of Heterocyclic Chemistry* **2014**, *51*, 1740–1746, doi:10.1002/jhet.1870.
36. Worrall, D.E. THE ADDITION OF 1,3-DIKETONES TO ISOTHIOCYANATES. I. ACETYLACETONE AND CERTAIN ARYL ISOTHIOCYANATES. *J. Am. Chem. Soc.* **1920**, *42*, 1055–1061, doi:10.1021/ja01450a020.
37. Borisevich, A.N.; Pel'kis, P.S. Arylamides of substituted thioacetic acids. *Chem Heterocycl Comp* **1972**, *5*, 237–239, doi:10.1007/BF00943927.
38. Kucharek, M.; Danel, A. Palladium-catalyzed amino group arylation of 1,3-disubstituted 1H-pyrazol-5-amine based on Buchwald–Hartwig reaction. *Chem Heterocycl Comp* **2021**, *57*, 633–639, doi:10.1007/s10593-021-02961-z.
39. Khachatryan, K.; Boszczyk, W.; Tomasik, P. Optical Properties of Some 4-Aryl-1H-pyrazolo[3,4-b]quinolines. *ChemInform* **2006**, *37*, doi:10.1002/chin.200607156.