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# PIFA-mediated synthesis of novel pyrazoloquinolin-4-ones as potential ligands for the estrogen receptor

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ABSTRACT

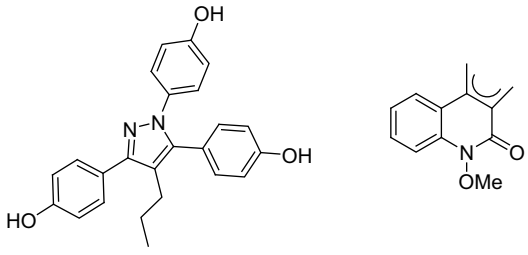
A facile and efficient preparation of pyrazoloquinolin-4-ones, as potential ligands for the estrogen receptor, via a PIFA [phenyliodine(III)bis(trifluoroacetate)] promoted cyclization reaction with overall yields up to 29% over six steps is described. The employed strategy, based on an electrophilic amidation reaction as the key step of the synthesis, allows the generation of a diverse array of derivatives.



Estrogens stimulate various biological functions via their molecular target, the estrogen receptor (ER, ERα and ERβ subtypes).[1,2] The latter acts as a ligand activated-transcriptional regulator that binds with a wide spectrum of steroidal and nonsteroidal ligands.[3] The structure of high ER affinity synthetic estrogens, especially those of nonsteroidal nature, generally consists of a phenolic functionality that mimics the phenol moiety of natural estradiol, and is tolerant to other target structural motifs that can be encompassed.[4–6]

Thus, intense research activity has been initiated toward the development of novel Selective Estrogen Receptor Modulators (SERMs) that possess high affinity and selectivity for an ER subtype and a broad variety of diverse ligands, based on various parameters and limitations,[7,8] have been considered. In this context, the incorporation of a pyrazole moiety in the structures studied represents an intriguing case, since the propylpyrazoletriol (PPT) **1** (Fig. 1), a 1,3,5-triaryl-4-alkyl-substituted pyrazole derivative, has been found to possess particularly high ERα-selective binding affinity and potency.[9]

As a part of our ongoing investigation concerning the development of novel SERMs, we were intrigued to explore the incorporation of fused heterocycle–pyrazole ring systems in this class of compounds. Our involvement was stimulated by the pronounced synthetic and biological interest[10,11] on pyrazole derivatives and




**PPT, 1** **2**

**Figure 1.** Propylpyrazoletriol (PPT) **1** and quinolinones of type **2**.

their utilization by the pharmaceutical and agrochemical industries.[12] The key step for the synthesis of the target compounds is a hypervalent iodine-promoted electrophilic amidation.

The use of hypervalent iodine compounds for synthetic purposes has gained significant interest. The low toxicity associated with these reagents in conjunction with the mild reaction conditions employed has resulted in their application in an increasing number of diverse transformations.[13] In this regard, research has focused on new applications of PIFA [phenyliodine(III)bis(trifluoroacetate)] for the efficient syntheses of various bioactive heterocycles. Thus, the syntheses of heterocycle-fused quinolinones of type **2** (Fig. 1), such as 1,4-diazepin-2-ones, isoquinolinone, and isoindolinone, have appeared in the literature.[14–16] This research

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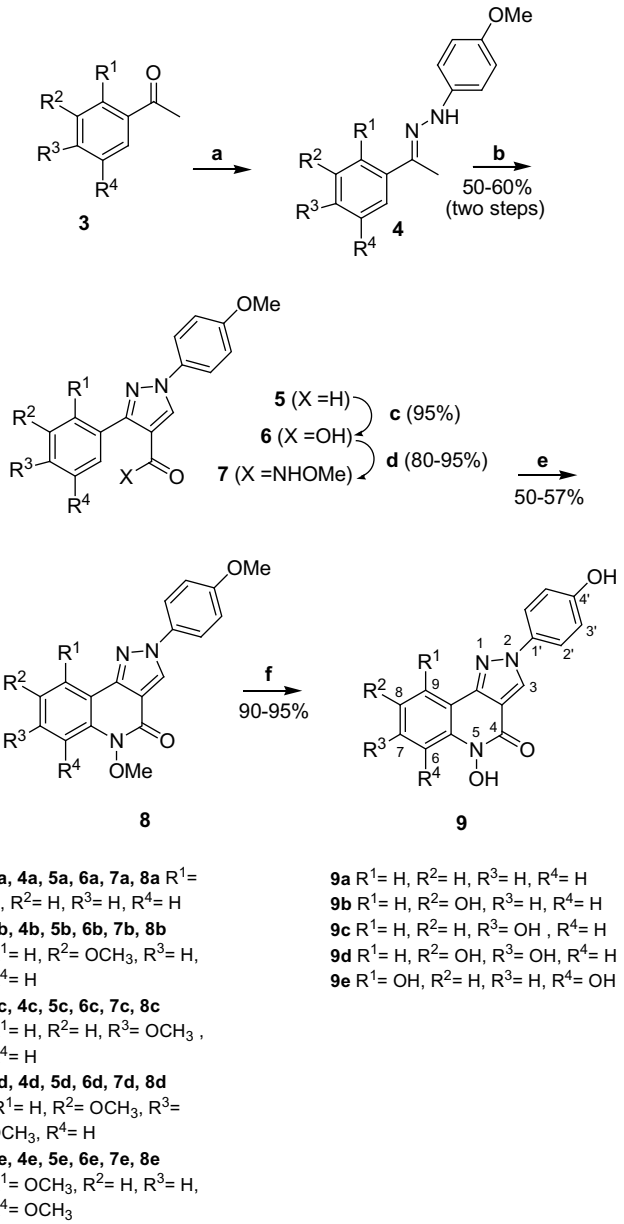
has now been extended, aimed at the development of a new approach for the preparation of novel pyrazoloquinolin-4-one derivatives with potential SERM activity.

The overall synthetic route utilized for the preparation of the target pyrazoloquinolin-4-ones **9** is depicted in Scheme 1. The first step refers to the condensation of various acetophenones **3** with 4-methoxyphenylhydrazine hydrochloride to provide efficiently the hydrazones **4**. Since hydrazones **4a–e** are highly labile, their formation was revealed through their crude NMRs. Thus, these derivatives were not isolated but transformed directly, without further purification, into the corresponding pyrazolocarboxaldehydes **5a–e** (Table 1) by treatment with the iminium salt formed from 2,4,6-trichloro(1,3,5)triazine (TCT, cyanuric chloride) and DMF.[17] It should be noted, however, that the use of Vilsmeier–Haack reaction conditions (DMF–$POCl_3$, 80 °C) resulted in the formation of only pyrazole **5a** ($R^1$, $R^2$, $R^3$, and $R^4$ = H), since for all other substrates thermal decomposition or degradation occurred. A




**Scheme 1.** Reagents and conditions: (a) 4-methoxyphenylhydrazine hydrochloride (1.0 equiv), THF; (b) TCT, DMF; (c) $NaClO_2$, $H_2NSO_3H$, acetone/$H_2O$, 0 °C; (d) $Et_3N$, $NH_2OMe{\cdot}HCl$, TBTU, MeCN; (e) PIFA, TFA, $CH_2Cl_2$; (f) $BBr_3$, $CH_2Cl_2$, −78 °C.

**Table 1**
Substitution patterns of compounds **5a–e**, **6a–e**, **7a–e**, **8a–e**, and **9a–e**, and their respective yields

| Product | $R^1$ | $R^2$ | $R^3$ | $R^4$ | X | Yield (%) |
|---|---|---|---|---|---|---|
| **5a** | H | H | H | H | H | 60 |
| **5b** | H | $OCH_3$ | H | H | H | 55 |
| **5c** | H | H | $OCH_3$ | H | H | 55 |
| **5d** | H | $OCH_3$ | $OCH_3$ | H | H | 50 |
| **5e** | $OCH_3$ | H | H | $OCH_3$ | H | 50 |
| **6a** | H | H | H | H | OH | 95 |
| **6b** | H | $OCH_3$ | H | H | OH | 95 |
| **6c** | H | H | $OCH_3$ | H | OH | 95 |
| **6d** | H | $OCH_3$ | $OCH_3$ | H | OH | 95 |
| **6e** | $OCH_3$ | H | H | $OCH_3$ | OH | 95 |
| **7a** | H | H | H | H | NHOMe | 95 |
| **7b** | H | $OCH_3$ | H | H | NHOMe | 90 |
| **7c** | H | H | $OCH_3$ | H | NHOMe | 90 |
| **7d** | H | $OCH_3$ | $OCH_3$ | H | NHOMe | 85 |
| **7e** | $OCH_3$ | H | H | $OCH_3$ | NHOMe | 80 |
| **8a** | H | H | H | H | — | 57 |
| **8b** | H | $OCH_3$ | H | H | — | 55 |
| **8c**[a] | H | H | $OCH_3$ | H | — | 55 |
| **8d** | H | $OCH_3$ | $OCH_3$ | H | — | 50 |
| **8e** | $OCH_3$ | H | H | $OCH_3$ | — | 50 |
| **9a** | H | H | H | H | — | 95 |
| **9b** | H | OH | H | H | — | 95 |
| **9c** | H | H | OH | H | — | 95 |
| **9d** | H | OH | OH | H | — | 90 |
| **9e** | OH | H | H | OH | — | 90 |

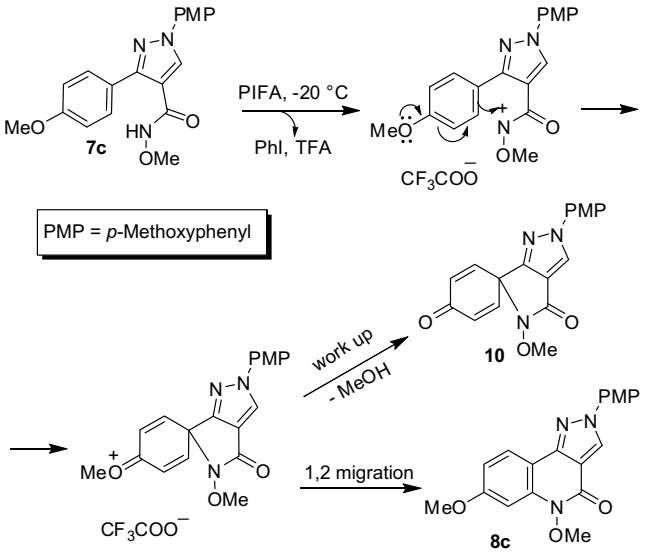
[a] The spiro compound **10** was also obtained (8%).

recent report concerning the formation and stability of these hydrazones, and their respective pyrazole derivatives has revealed the impact of a rise in temperature and/or the crucial role of microwave irradiation, which seriously affects the reaction yield.[17] It is evident that in this case, the substitution pattern of both the acetophenone and phenylhydrazine ring plays a pivotal role in the stability of the derived molecules, since the reaction with TCT was carried out at room temperature without the use of microwave-assisted methodologies. Furthermore, the presence of methoxy substituents on the aromatic rings, in contrast with electron-withdrawing substituents, such as a nitro group,[18] differentiates the chemical behavior and stability of the intermediate hydrazones **4**.

Next, the aldehydes **5a–e** were oxidized with $NaOCl_2$ in the presence of sulfamic acid as a scavenger, producing, almost quantitatively, the corresponding carboxylic acids **6a–e**. The latter were converted into the respective amides, **7a–e**, by reaction with methoxylamine hydrochloride in the presence of the uronium coupling reagent TBTU. To promote the cyclization step, PIFA was selected as the source of hypervalent iodine to induce the generation of the expected acylnitrenium intermediates. In this context, when using trifluoroacetic acid (TFA) as additive and $CH_2Cl_2$ as solvent, the pyrazoloquinolin-4-ones **8a–e** were obtained in moderate to good yields (50–57%).[19]

Additional experiments using trifluoroethanol as solvent produced the same reaction products in lower yields (~35%). It should be noted that under these conditions, the use of amide **7c** as substrate resulted in the formation of two reaction products (quinoline **8c** and the fused-spiro product **10**, Scheme 2). The co-formation of these compounds can be rationalized considering that they are being obtained through the same pathway via the formation of the same intermediate, which may either be hydrolyzed during the work-up process or via a 1,2-migration process, which is transformed into a quinoline.[20,21] NOESY experiments proved the proposed structure for product **8c**, over other possible regioisomers, through correlations of H-6 with the N–$OCH_3$ and the C7–$OCH_3$ groups.

Finally, the demethylation of the methoxy-protective groups with $BBr_3$ at −78 °C in $CH_2Cl_2$ provided the desired quinolin-4-ones **9** in almost quantitative yields (90–95%) (Table 1).




**Scheme 2.** Proposed mechanistic pathway for the formation of spiro compound **10** and quinolinone **8c**.

## Acknowledgments

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19. General procedure for the cyclization of amides **7a–e** with PIFA: A solution of PIFA (0.28 g, 0.64 mmol) and TFA (0.10 mL, 1.3 mmol) in $CH_2Cl_2$ (9 mL) was added to a cold (−20 °C) solution of amide **7** (0.42 mmol) in $CH_2Cl_2$ (4 mL). The mixture was stirred at the same temperature until total consumption of the starting material (TLC, 1 h). The reaction mixture was quenched with 10% aq $Na_2CO_3$, and extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic layers were washed with a saturated solution of NaCl, dried over $Na_2SO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/EtOAc, 3/7) to furnish the desired quinolinone **8**.
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