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Pyridazinone derivatives: Design, synthesis, and in vitro vasorelaxant activity

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Abstract—In an attempt to identify potential vasodilator–cardiotonic lead compounds, three series of pyridazinones were designed using three-dimensional pharmacophore developed with CATALYST software from a set of potent cyclic nucleotide phosphodiesterase III, cAMP PDEIII inhibitors. The features of the target compounds were based on the structures of many biologically active lead compounds with cAMP phosphodiesterase III inhibiting activity such as Milrinone and others. Compounds with higher fit scores to the developed pharmacophore were synthesized namely; 6-(3-ethoxycarbonyl-4-oxo-1,4-dihydroquinolin-6-yl)-4,5-dihydro-3(2*H*)-pyridazinones (**3a** and **3b**), 6-[4-(2,6-disubstituted-quinolin-4-ylamino)phenyl]-4,5-dihydropyridazin-3(2*H*)-ones (**5a**–**f**), and 6-[3-(5-cyano-6-oxo-4-aryl-1,6-dihydro-2-pyridyl)phenylamino]-3(2*H*)pyridazinone (**8a** and **8b**). The vasodilator activity of the newly synthesized compounds was examined on the isolated main pulmonary artery of the rabbit. Some of the tested compounds showed moderate vasorelaxant activity compared with standard drug, Milrinone.

1. Introduction

Congestive heart failure is one of the most life-threatening syndrome.[1] Digoxin has been used for treatment of the failing heart for many years. The toxic side-effects of digoxin have encouraged the scientists to develop an alternative therapy.[2–4a] Intensive research efforts in this area have led to the discovery of few medicinally important cardiotonic agents. Inhibition of cAMP PDE III leads to elevated level of cAMP which acts through a complex chain of biochemical events to an increase in intracellular calcium and ultimately an increase in muscle contractility and peripheral vasodilatation.[4b] Amirinone is the first breakthrough in this field.[5] Afterward, research has been intensified aiming to identify more potent and safer congeners which led to discovery and modeling of Milrinone analogs.[6,7] Several pyridazinone derivatives were developed as structurally relevant aza analogs for amirinone.[8–11] Consequently, five point models and pharmacophores were identified for these agents and their mechanism of action was also established.[12–14] Later on, many of these compounds acting through inhibition of cyclic nucleotide phosphodiesterase III isozyme of cAMP-PDE III isolated from heart muscle consist of a pyridazinone ring attached to a substituted aromatic nucleus. In a subset of these compounds, typified by indolidan[15] and bemoradan,[16] primobendan,[17] the pyridazinone ring is attached to a benzo-fused heterocycle. The nature of this benzo-fused heterocyclic fragment of the molecule would seem to be important to physical properties as well as the biological effects, metabolism, and distribution of the compounds.[18,19a]

Several modeling studies in the field of PDE inhibitors led to recognition of the active site of the enzyme as well as pharmacophoric pattern of these agents. A review on the crystal structures of the catalytic domains of phosphodiesterase (PDE) families discussed how this structural information has provided the basis for the design of potent and selective PDE inhibitors. Later on, preliminary X-ray diffraction analysis of the catalytic domain of recombinant human phosphodiesterase 3B and, the catalytic domain of human cAMP

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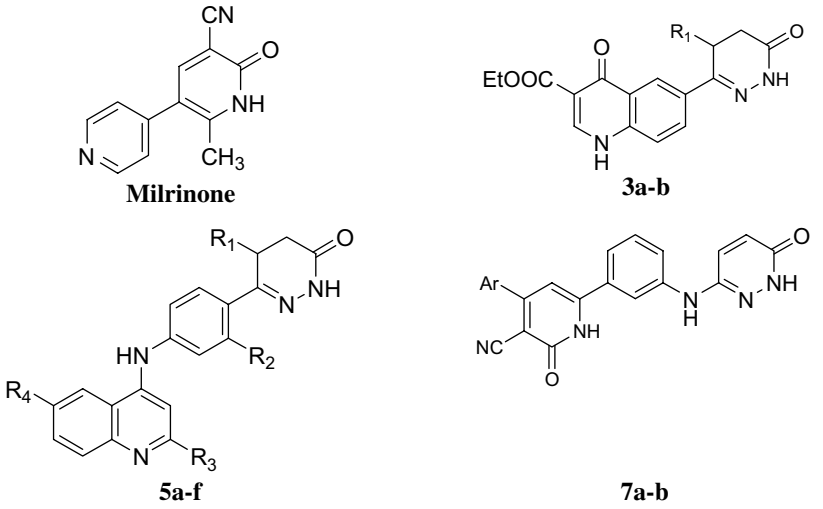


Figure 1. Some representative examples of the designed compounds and the lead compound.

phosphodiesterase 3B (PDE3B) was cloned, and purified in the presence of the PDE3 inhibitors, IBMX (3-isobutylmethylxanthine) or MERCK1 by affinity chromatography.[19b–d]

In the same direction toward development of safe, selective potent cardiotonic–vasodilator agent, we designed and synthesized three series of structurally relevant compounds derived from the pharmacophoric pyridazinone residue. The first series of these compounds are designed so that the pyridazinone is linked directly to quinolone nucleus. The second series engages both pyridazinone ring and substituted quinolines via aminophenyl spacer. In the last set of compounds, we have combined both pyridazinone and pyridone ring systems linked via aminophenyl moiety (Fig. 1). Molecular modeling studies were performed on the designed compounds using Catalyst-HipHop software package in our facility provided by accylrs®.[20] This was fulfiled by mapping different target pyridazinone compounds to the hypothesis generated from eight known cyclic nucleotide phosphodiesterase III, cAMP PDEIII inhibitors in order to predict and rank these compounds according to their fit values to hypothesis model (Table 1).[21] Finally, vasorelaxant activity for the synthesized compounds was studied in vitro on isolated main pulmonary artery of the rabbit.

Table 1. 'Fit' scores and conformational energies of the test compounds by mapping onto pharmacophore model of cAMP-PDE inhibitors

Compound	Conformational energy in kcal/mol (No. of conformers)	Fit score
3a	19.6669 (33)	3.9042
3b	18.127 (41)	3.89
5a	1.71148 (65)	3.9803
5b	1.788 (66)	3.970
5c	0.766 (63)	3.98
5d	6.44 (28)	3.9673
5e	1.2275 (51)	3.9934
5f	2.3388 (47)	3.998
8a	11.624 (118)	3.7823
8b	13.9383 (64)	3.75
MCI-154	0	3.998

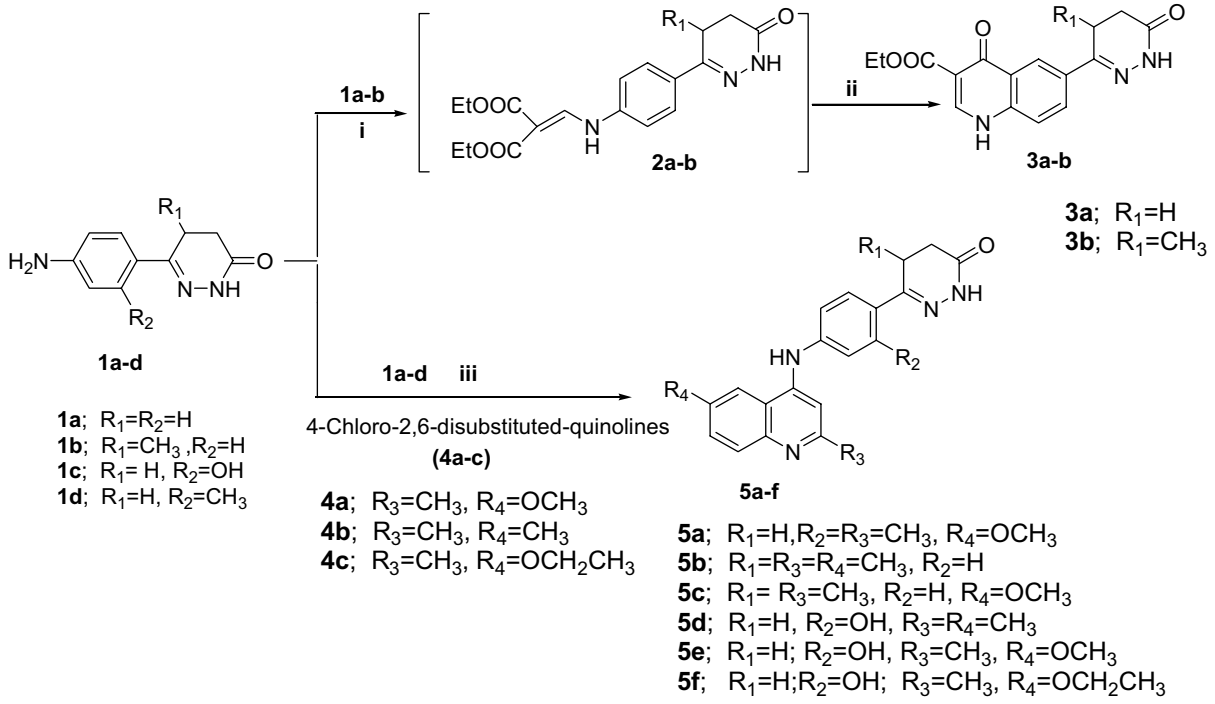
2. Chemistry

Scheme 1 summarizes the synthesis of compounds **3**–**5**. Briefly, the intermediates diethyl 2-[(4-(6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenylamino)methylene]malonate (**2a** and **2b**) were prepared via nucleophilic addition of the corresponding 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2*H*)-ones (**1a** and **1b)** to β carbon of diethyl ethoxymethylenemalonate followed by facile elimination of ethanol. The crude diester was heated in diphenyl ether whereas cyclization to the quinolone ester **3a** and **3b** takes place with elimination of ethanol in a moderate yield. The formation of **3a** and **3b** was confirmed by ^{1}H NMR and mass spectra where they were in conformity with assigned structure.

Compounds **5a**–**f** were obtained in a good yield through the nucleophilic displacement of chlorine atom of the 4-chloroquinoline derivatives (**4a**–**c**) with the corresponding aminophenylpyridazinones **1a**–**d**.

Synthesis of compounds **8a**–**b** is depicted in Scheme 2 wherein, 6-(3-acetylphenylamino)-3-chloropyridazine **6** was obtained through the reaction of 3,6-dichloropyridazine and 3-aminoacetophenone in ethanol in a good yield. Hydrolysis of compound **6** was carried out upon heating in glacial acetic acid to afford the pyridazinone derivative **7**. The formation of **7** was confirmed by IR spectra of two C=O signals at 1680 and 1670 cm^{-1}.

2-Oxo-6-[3-(6-oxo-1,6-dihydropyridazin-3-ylamino)aryl]-4-phenyl-1,2-dihydropyridine-3-carbonitrile (**8a** and **8b)** were synthesized in a similar manner described before[7] through the reaction of the acetophenone derivative **7** with the appropriate aldehyde namely 3-pyridinecarbox-



Scheme 1. Reagents and conditions: (i) diethyl ethoxymethylenemalonate, ethanol, reflux; (ii) diphenyl ether, 150 °C; (iii) *n*-butanol, reflux.

aldehyde, 3-nitrobenzaldehyde, and ethyl cyanoacetate in presence of ammonium acetate and ethanol. The structure of **7** was verified by IR, ^{1}H NMR, and MS. The IR spectra of compounds **8a** and **8b** showed the characteristic absorption band of CN at 2200 cm^{-1}. The ^{1}H NMR and MS spectra of them were basically in agreement with their proposed structures.

The synthesis of the newly designed products is described in Schemes 1 and 2.

3. Molecular modeling study

Pharmacophore mapping is one of the major elements of drug design; it is initially applied to discovery of lead molecules and now extends to lead optimization. Pharmacophores can also be used as queries for retrieving potential leads from structural databases (*lead discovery*), for designing molecules with specific desired attributes (*lead optimization*) and for assessing similarity and diversity of molecules using pharmacophore finger-prints.[21]

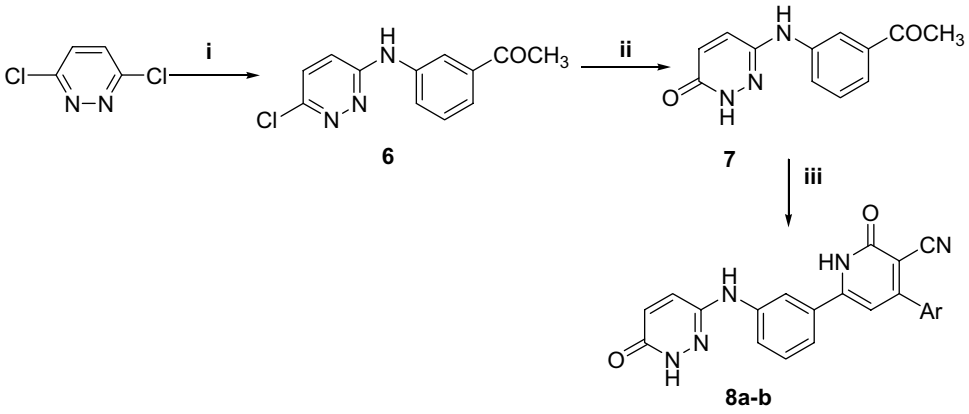
In the area of drug discovery, it was previously reported that the salient features strictly necessary for cardiotonic activity[12–14] via PDEase III inhibition are:

(a) Strong dipole (carbonyl group of the lactam moiety) at one end of the molecule
(b) An adjacent acid proton
(c) An electron-rich center and or a hydrogen bond acceptor site opposite to the dipole
(d) Distance of 5 Å between the amidic N and center of the phenyl ring.

Since, no previous pharmacophore was known to PDEase III inhibitors, therefore, in the present study, we aim to generate three-dimensional pharmacophore (hypothesis) for cAMP PDE III inhibitors, using *Catalyst-HipHop* module, which could be used as a template for identifying new leads in this area. The generated pharmacophore was developed from a training set of eight potent cAMP PDE III inhibitors (Fig. 2).

It was found that this hypothesis consists of four features: two hydrogen bond acceptor (HBA) appeared as a vector (green spherical mesh), positive ionizable function (PI) (violet spherical mesh), and hydrophobic functions (white spherical mesh) (Fig. 3).

During pharmacophore development, the molecules were mapped to the features with pre-determined conformations generated using the ''the fast fit'' techniques in the catalyst. The procedure resulted in the generation of nine alternative pharmacophores for cAMP PDE III inhibitors and appeared to perform quite well for the training set. Significantly, the best pharmacophore characterized by two hydrogen bond acceptor functions, positive ionizable function (PI), and hydrophobic functions (Fig. 3) is also statistically the most relevant pharmacophore. We mapped the pharmacophore on known cAMP PDE III inhibitors in order to utilize the information for identifying the target and to design more potent inhibitors. This indirect approach for drug design was used to explore and predict the activity and rationalize the effect of different spacers between the pyridazinone ring and heteroaromatic ring system on their mapping scores. In this case the conformational model for each lead compound was generated and then used to construct the common-feature hypothesis (by default). The generated hypothesis was used as a



Scheme 2. Reagents and conditions: (i) *m*-$NH_2C_6H_4COCH_3$, ethanol, reflux; (ii) AcOH, reflux; (iii) ArCHO, $CNCH_2COOEt$, CH_3COONH_4, ethanol, reflux.

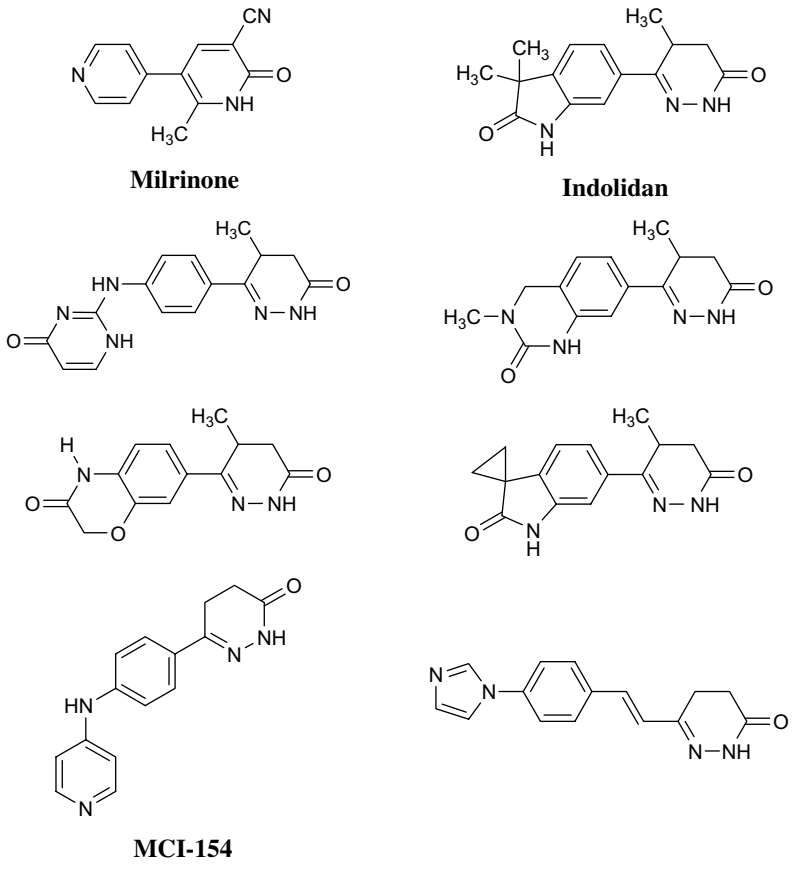


Figure 2. Training set of selected potent cAMP-Phosphodiesterase III inhibitors.

template to predict the activity of the target compounds (Figs. 4–7).

4. Evaluation of vasorelaxing activity in vitro

In the present work, we have investigated the potential vasorelaxant effects of a series of new pyridazine derivatives **3a**, **3b**, **5a–f**, **8a**, and **8b** in main pulmonary artery of the rabbit.

It has been reported that the intracellular activity of the vasorelaxant effects of the compounds tested may also be indirect, due to an increase in cytosolic cyclic nucleotide levels (mainly cGMP) through inhibition of the different phosphodiesterase subtypes described in vascular smooth muscle.[22]

Therefore, inhibition of cAMP PDE can be assessed indirectly through measuring the vasorelaxant effect of the test compounds.

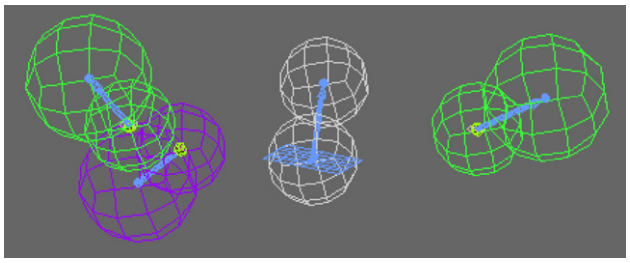


Figure 3. Pharmacophore for cAMP PDE III inhibitors.

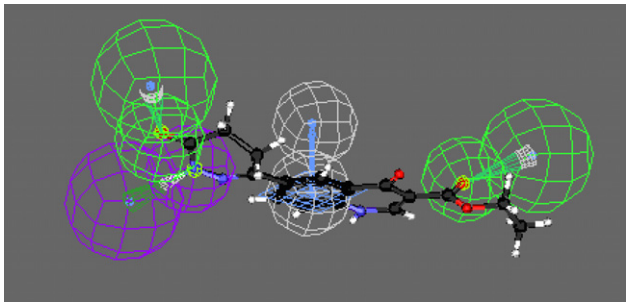


Figure 4. Mapping of **3a** onto the cAMP-PDE inhibitors pharmacophore model.

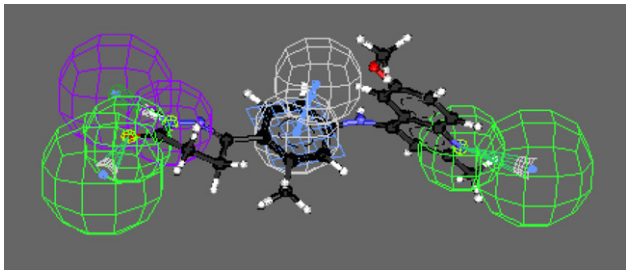


Figure 5. Mapping of **5a** onto the cAMP-PDE inhibitors pharmacophore model.

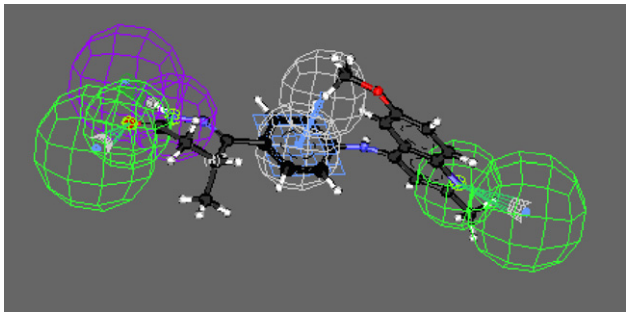


Figure 6. Mapping of **5c** onto the cAMP-PDE inhibitors pharmacophore model.

4.1. Drugs and chemicals

The following drugs and chemicals were used in this study:

Milrinone (Boehringer Ingelheim Co, Ingelheim am Rhein), DMSO (Sigma Chemical Co., St. Louis, MO). All other reagents were of analytical grade.

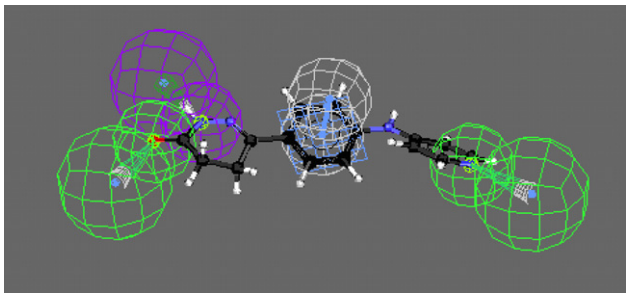


Figure 7. Mapping of MCI-154 onto the cAMP-PDE inhibitors pharmacophore model.

4.2. Methods

The experiments have been carried out in the isolated main pulmonary artery of the rabbit.[23] The main pulmonary artery (weight, 40–80 mg) was dissected and placed into normal Kerbs solution which contains 8 mM potassium chloride to check the vasorelaxing activity and which was fully equilibrated with carbogene (5% CO_2 in O_2, pH 7.4). Then the artery was opened longitudinally, fixed by two threads in such a way that the circular muscle fibres were running between the threads, and placed into a loading bath (volume, 1.5 ml) for 30 min at 37 °C. After thorough washing, this process was repeated until the amplitude of the concentrations became constant. The substances were investigated using the single dose technique at concentration of 10^{-4} M. Compounds are dissolved in DMSO and diluted with distilled water to the appropriate volume. The preparations were washed until the initial situation reestablished and potassium chloride concentrations were induced. The concentrations of potassium chloride for each compound under test were recorded with 96 Transducer Data Acquisition System (Cairo, Egypt).

4.3. Data and statistical analysis

Data were expressed as means ± SE. Statistical comparison between different groups was performed using one-way analysis of variance (ANOVA) followed by the multiple comparison test. Significance was accepted at $p < 0.05$.

4.4. Results and discussion

In Table 2 the vasodilator activity of compounds **3a**, **3b**, **5a**–**f**, **8a**, and **8b** is presented. Data revealed that pyridazinone compounds **5e** and **5f** exhibited the highest in vitro vasorelaxant activity among 4-aminoquinoline series. They inhibited the contraction obtained with 8 mM KCl by 34.33% and 36.17%, respectively, compared with Milrinone as a control vasodilator agent which showed 60.5% inhibition. However, compounds **8a** and **8b** showed only weak vasorelaxant activity. Unfortunately, no correlation between the substituents and biological activities of the compounds was noticeable.

It is obvious from molecular mapping study that both compounds **5e** and **5f** possess higher fit value to the pharmacophoric model for cAMP PDE inhibitor as both of them

Table 2. Vasorelaxant activity of the test compounds

Compound (10^{-4} M)	% Inh. of KCl contraction (8 mmol) means ± SE
Milrinone	*60.50 ± 1.34
3a	*14.50 ± 1.18
3b	*14.50 ± 0.89
5a	*25.00 ± 1.46
5b	*22.67 ± 1.45
5c	*21.50 ± 1.61
5d	*18.50 ± 1.31
5e	*34.33 ± 1.20
5f	*36.17 ± 1.49*
8a	*8.17 ± 0.56
8b	*9.10 ± 0.50

*Significantly different from Milrinone value at $P < 0.05$.

possess phenolic OH group on phenyl group and alkoxy group at the 6th position of quinoline ring which make their mapping to the pharmacophoric model optimum and hence their in vitro activity is higher. On the other hand, both, compounds **8a** and **8b**, possess less score in mapping study, also the low activity could be attributed in part to their poor solubility in organ bath medium.

5. Experimental

Melting points were obtained on Graffin apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 435 Spectrometer, using KBr disks. ^{1}H NMR spectra were recorded on a Perkin-Elmer NMR FXQ-200 MHZ Spectrometer, using TMS as internal standard. Mass spectra were recorded on a GCMS-QP 1000 EX, Mass Spectrometer. Elemental analyses for C, H, and N were within ±0.4% of the theoretical values and were performed at the Microanalytical Center, Cairo University, and they were of the theoretical values. Progress of the reactions was monitored by TLC using precoated aluminum sheets silica gel MERCK 60 F 254 and was visualized by UV lamp.

6-(4-Aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinones (**1a**–**d**) were prepared according to reported methods[24–26] and 4-chloro-2,6-disubstituted-quinolines were also prepared according to methods in literature.[27–30] All other chemicals were purchased from Aldrich, Fluka, Acros, and Merck companies.

5.1. General procedure for compounds 3a and 3b

To a solution of the proper aminophenylpyridazinone derivatives **1a**–**b** (0.002 mol) in ethanol (20 ml), diethyl ethoxymethylenemalonate (0.43 ml, 0.002 mol) was added and the mixture was heated under reflux for 4 h. The precipitate formed was filtered, dried, and dissolved in diphenyl ether (50 ml). The reaction mixture was heated at 150 °C in an oil bath for 3 h. On cooling, the solid obtained was filtered, washed with benzene 10 × 3, dried, and crystallized from dimethylformamide.

5.1.1. Ethyl 6-(6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (3a). The title compound was prepared from the reaction of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2*H*)-one (**1a**) and diethyl ethoxymethylenemalonate to give **2a** and its cyclization in diphenyl ether provides **3a**.

Yield, 80%; mp 303–305 °C; ^{1}H NMR (DMSO-d_6) δ 1.28 (t, 3H, J = 7 Hz, CH_3CH$_2$OO), 2.49 (t, 2H, J = 8, CH$_2$ pyridazine), 3.02 (t, 2H, J = 8 Hz, CH$_2$pyridazine), 4.19–4.26 (q, 2H, J = 7 Hz, CH$_3$CH_2OO), 7.64 (d, 1H, J = 8.6 Hz, aromatic H), 8.13 (d, 1H, J = 8.6, aromatic H), 8.42 (s, 1H, aromatic-H), 8.54 (d, 1H, J = 14 Hz, quinolone C2 H), δ 11.02 (d, 1H, J = 14 Hz, NH quinolone, D$_2$O exchangeable), 12.46 (s, 1H, NH, pyridazine, D$_2$O exchangeable); IR(KBr) cm^{-1}: 3400, 3200 (NH), 1700, 1630, 1620 (3C=O); MS m/z 313 (M$^+$).

5.1.2. Ethyl 6-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)-4-oxo-1,4- dihydroquino-line-3-carboxylate (3b). The title compound was prepared from the reaction of **1b** and diethyl ethoxymethylenemalonate to give **2b** followed by cyclization in diphenyl ether. Yield 75%, mp 220–222 °C; ^{1}H NMR (DMSO-d_6), δ 1.12 (d, 3H, J = 7.4 Hz, CH_3CH), 1.28 (t, 3H, J = 7.4 Hz, CH_3CH$_2$COO), 2.23 (d, 1H, J = 17 Hz, CH pyridazine), 2.69–2.82 (dd, 1H, J = 6.8 Hz, CH pyridazine), 3.48–3.55 (m, 1H, J = 7 Hz, CH–CH$_3$, pyridazine), 4.23 (q, 2H, J = 7.4 Hz, CH$_3$CH_2COO), 6.99 (d, 1H, J = 7.6 Hz, aromatic H), 7.37 (d, 1H, J = 7.6 Hz, aromatic H), 7.8 (s, 1H, aromatic H), 8.40 (d, 1H, J = 14 Hz, quinolone C2 H), 11.03 (d, 1H, J = 14, NH quinolone D$_2$O exchangeable), 11.90 (s, 1H, NH pyridazine D$_2$O exchangeable); IR(KBr) cm^{-1}: 3400, 3200 (NH), 1700, 1630, 1620 (3C=O); MS m/z (M−2, 325).

5.2. General procedure for compounds (5a–f)

To a solution of the proper **1a**–**d** (0.01 mol) in *n*-butanol (20 ml), the appropriate 4-chloroquinoline **4a**–**c** (0.01 mol) was added and the mixture was heated under reflux for 4 h. The formed precipitate was filtered while hot, washed with ethanol, sodium carbonate solution, and recrystallized from dimethylformamide.

5.2.1. 6-[2-Methyl-4-(6-methoxy-2-methylquinolin-4-ylamino)phenyl)]-4,5-dihydro-3(2*H*)-pyridazinone (5a). The title compound was prepared from the reaction of **1d** with 4-chloro-6-methoxy-2-methylquinoline (**4a**) in 85% yield; mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 2.44 (s, 3H, CH$_3$), 2.47 (t, 2H, J = 8 Hz, CH$_2$,pyridazinone), 2.6 (s, 3H, CH$_3$), 2.89 (t, 2H, J = 8 Hz, CH$_2$ pyridazinone), 3.98 (s, 3H, OCH$_3$), 6.78 (s, 1H, aromatic), 7.36 (br s, 2H, aromatic H), 7.54 (d, 1H, J = 8.7 Hz, aromatic H), 7.64 (d, 1H, J = 8.9 Hz, aromatic H), 7.97 (d, 1H, J = 9 Hz, aromatic H), 8.16 (s, 1H, aromatic), 10.62 (s, 1H, NH, D$_2$O exchangeable), 10.96 (s, 1H, NH pyridazinone, D$_2$O exchangeable); IR(KBr) cm^{-1}: 3200, 3150 (NH), 1670 (C=O); MS m/z: 374 (M$^+$).

5.2.2. 6-[4-(2,6-Dimethylquinolin-4-ylamino)phenyl)-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (5b). The title compound was prepared from the reaction of **1b** with 4-chloro-2,6-dimethylquinoline (**4b**) in 60% yield. Mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 1.23 (d, 3H, J = 7 Hz, CH$_3$CH), 2.26 (d, 1H, J = 17 Hz, CH pyrida-

zine), 2.56 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.70–2.77 (dd, 1H, $J = 7$ Hz, CH pyridazine), 3.43–3.45 (m, 1H, CH–CH_3 pyridazine), 6.86 (s, 1H, aromatic H), 7.52–7.55 (d, 2H, $J = 8.1$ Hz, aromatic H), 7.83–7.86 (d, 1H, $J = 8.4$ Hz, aromatic H), 7.90–7.93 (d, 1H, $J = 8.4$ Hz, aromatic H), 7.95–7.97 (d, 2H, $J = 8.1$ Hz, aromatic H), 8.53 (s, 1H, aromatic H), 10.62 (s, 1H, NH, D_2O exchangeable), 11.06 (s, 1H, NH, D_2O exchangeable) IR(KBr) cm^{-1}: 3200, 3150 (NH), 1680 (C=O); MS *m/z*: 358 (M^+).

5.2.3. 6-[4-(6-Methoxy-2-methylquinolin-4-ylamino)phenyl)-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (5c). The title compound was prepared from the reaction of **1b** with 4-chloro-6-methoxy-2-methylquinoline (**4a**) in 83% yield. Mp > 300 °C; ^1H NMR(DMSO-d_6) δ 1.23 (d, 3H, $J = 7$ Hz, CH_3CH), 2.29 (d, 1H, $J = 17$ Hz, CH pyridazine), 2.6 (s, 3H, CH_3), 2.7–2.77 (dd, 1H, $J = 6.8$), 3.46–3.55 (m, 1H, $J = 7$, CH pyridazine), 3.98 (s, 3H, OCH_3), 6.84 (s, 1H, aromatic), 7.54–7.56 (d, 2H, $J = 8.2$ Hz, aromatic H), 7.63–7.66 (d, 1H, $J = 9$ Hz, aromatic H), 7.95–7.99 (m, 3H, aromatic H), 8.17 (s, 1H, aromatic H), 10.67 (s, 1H, NH D_2O, exchangeable), 11.06 (s, 1H, NH pyridazine, D_2O exchangeable); IR(KBr) cm^{-1}: 3200, 3150 (NH), 1680 (C=O); MS *m/z*: 374 (M^+).

5.2.4. 6-[3-Hydroxy-4-(2,6-dimethylquinolin-4-ylamino)phenyl)-4,5-dihydro-3(2*H*)-pyridazinone (5d). The title compound was prepared from the reaction of **1c** with 4-chloro-2,6-dimethylquinoline (**4b**) in 75% yield. Mp 250–252 °C; ^1H NMR (DMSO-d_6), δ 2.43–2.45 (t, 2H, $J = 8$ Hz, CH_2 pyridazine), 2.54 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), δ 2.92–2.94 (t, 3H, $J = 8$ Hz, CH_2 pyridazine), 6.2 (s, 1H, aromatic H), 7.14 (d, 1H, $J = 8.4$ Hz, aromatic H), 7.6–7.72 (s, 1H aromatic H, and d, 1H, $J = 8$ Hz aromatic H), 7.81–7.9 (dd, 2H, $J = 8$ Hz, aromatic H), 8.5 (s, H, aromatic H), 10.35 (s, 1H, NH, D_2O exchangeable), 10.53 (s, 1H, phenolic OH, D_2O exchangeable), 10.86 (s, 1H, NH pyridazine, D_2O exchangeable); IR(KBr) cm^{-1}: 3300 (OH), 3200, 3150 (NH), 1670 (C=O); MS *m/z*: 360 (M^+).

5.2.5. 6-[2-Hydroxy-4-(6-methoxy-2-methylquinolin-4-ylamino)phenyl)]-4,5-dihydro-3(2*H*)-pyridazinone (5e). The title compound was prepared from the reaction of **1c** with 4-chloro-6-methoxy-2-methylquinoline (**4a**) in 85% yield. Mp 298–300 °C; ^1H NMR(DMSO-d_6), 2.40–2.43 (t, 2H, $J = 8$ Hz, CH_2 pyridazine), 2.53 (s, 3H, CH_3), 2.90–2.93 (t, 3H, $J = 8$ Hz, CH_2 pyridazine), 3.96 (s, 3H, OCH_3), 6.21 (s, 1H, aromatic H), 7.13–7.16 (d, 1H, $J = 9$ Hz, aromatic H), 7.61–7.64 (d, 1H, $J = 9$ Hz aromatic H), 7.69–7.72 (s, 1H, aromatic H and d, 1H, $J = 8$ Hz, aromatic H), 7.89–7.92 (d, 1H, $J = 9$ Hz, aromatic H), 8.09 (s, 1H, aromatic H), 10.31 (s, 1H, NH, D_2O exchangeable), 10.54 (s, 1H, phenolic OH, D_2O exchangeable), 10.87 (s, 1H, NH pyridazine, D_2O exchangeable); IR(KBr) cm^{-1}: 3350 (OH), 3300, 3200 (NH);1670 (C=O); MS *m/z*: 376 (M^+).

5.2.6. 6-[2-Hydroxy-4-(6-ethoxy-2-methylquinolin-4-ylamino)phenyl)]-4,5-dihydro-3(2*H*)-pyridazinone (5f). The title compound was prepared from the reaction of **1c** with 4-chloro-6-ethoxy-2-methylquinoline (**4c**) in 82% yield. Mp 230–232 °C ; ^1H NMR (DMSO-d_6) δ 1.43 (t, 3H, $J = 7$ Hz, CH_3CH_2O), 2.43–2.45 (t, 2H, $J = 8.5$ Hz, CH_2 pyridazine), 2.55 (s, 1H, CH_3), 2.92–2.95 (t, 2H, $J = 8.4$ Hz, CH_2 pyridazine), 4.23 (q, 2H, $J = 7$, H_2, CH_3CH_2O), 6.2 (s, 1H, aromatic), 7.14–7.16 (d, 1H, $J = 8.4$ Hz, aromatic H), 7.61–7.63 (d, 1H, $J = 9$ Hz, aromatic H), 7.68–7.20 (s, 1H, aromatic H and d, 1H, $J = 9$ Hz, aromatic H), 7.91–7.93 (d, 1H, $J = 9$ Hz, aromatic H), 8.07 (s, 1H, aromatic H), 10.29 (s, 1H, NH, D_2O exchangeable), 10.55 (s, 1H, OH, D_2O exchangeable), 10.87 (s, 1H, NH pyridazine, D_2O exchangeable); IR (KBr) cm^{-1}: 3300 (OH), 3200, 3150 (NH); 1660 (C=O); MS *m/z*: 390 (M^+).

5.3. 6-(3-Acetylphenylamino)-3-chloropyridazine (6)

A mixture of 3,6-dichloropyridazine (1.48 g, 0.01 mol) and 3-aminoacetophenone (1.35 g, 0.01 mol) in ethanol (30 ml) was heated under reflux for 4 h. The reaction mixture was evaporated under reduced pressure to half its volume. After cooling, the formed precipitate was filtered, dried, and recrystallized from isopropanol to give **6** in 75% yield. Mp 158 °C. ^1H NMR((DMSO-d_6) δ 2.64 (s, 3H, CH_3), 7.27–7.31(d, 1H, $J = 9.2$ Hz, pyridazine H), 7.51–7.59 (t, 1H, $J = 7.8$ Hz, Aromatic H), 7.69–7.65 (d, 1H, $J = 9.2$ Hz, pyridazine H), 8.04–8.08 (dd, 2H, $J = 8$ Hz, Aromatic H), 8.34 (s, 1H, Aromatic H), 9.75 (s, 1H, NH, D_2O exchangeable). IR(KBr) cm^1: 3350 (NH), 1680 (C=O), MS *m/z* (247, 32.33%) (249, 11.57%).

5.4. 6-[3-Acetylphenylamino]-3(2*H*)pyridazinone (7)

Compound **6** (2.47 g, 0.01 mol) was heated under reflux in glacial acetic acid (25 ml) for 5 h. The reaction mixture was evaporated to half its volume and then cooled. The formed precipitate was filtered, washed with water, and recrystallized from ethanol to give **6** in 65% yield. Mp 180 °C; ^1H NMR(DMSO-d_6) δ 2.56 (s, 3H, CH_3), 6.83–6.86 (d, 1H, $J = 9.8$ Hz, CH pyridazine), 7.17–7.21 (d, 1H, $J = 9.9$ Hz, CH pyridazine), 7.41–7.44 (d, 1H, $J = 7.8$ Hz, aromatic H), 7.50–7.52 (t, 1H, $J = 7.5$ Hz, aromatic H), 7.78–7.80 (d, 1H, $J = 8.1$ Hz, aromatic H), 8.08 (s, 1H, aromatic H), 9.17 (s, 1H, NH, D_2O exchangeable), 12.11 (s, 1H, NH pyridazine, D_2O exchangeable). IR (KBr) cm^{-1}: 3250, 3200 (NH), 1680, 1670 (2C=O).

5.5. General procedure for compounds 8a and 8b

A mixture of **7** (0.229 g, 0.001 mol), ethyl cyanoacetate (1.13 g, 0.001 mol), the proper aromatic aldehyde (0.001 mol), ethanol (40 ml), and ammonium acetate (0.616 g, 0.008 mol) in ethanol (40 mL) was heated under reflux for 9 h. The resulting precipitate was filtered, washed with water, and recrystallized from ethanol/dimethylformamide mixture (1:1).

5.5.1. 2-Oxo-6-[3-(6-oxo-1,6-dihydropyridazin-3-ylamino)phenyl]-4-(3-pyridyl)-1,2-dihydropyridine-3-carbonitrile (8a). The title compound was prepared from the reaction of **7** with 3-pyridinecarboxaldehyde, ethyl cyanoacetate, and ammonium acetate in 40% yield.

Mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 6.8 (m, 1H, aromatic H), 6.84–6.87 (d, 1H, J = 10 Hz, CH pyridazine), 7.21–7.23 (d, 1H, J = 10 Hz, CH pyridazine), 7.41–7.46 (m, 2H, aromatic H), 7.6–7.68 (m, 2H, aromatic H), 7.98 (s, 1H, aromatic H), 8.17 (d, 1H, J = 7.8 Hz, aromatic H), 8.76 (d, 1H, J = 4.6 Hz, aromatic H), 8.92 (s, 1H, aromatic H), 9.18 (s, 1H, NH, D_2O exchangeable), 12.13 (s, 1H, NH pyridazine, D_2O exchangeable), 12.93 (s, 1H, NH pyridone, D_2O exchangeable); IR(KBr) cm^{-1}: 3400, 3350 (NH), 2200 (CN), 1680, 1660 (2C═O); MS *m*/*z*: 382(M)$^+$.

5.5.2. 2-Oxo-6-[3-(6-oxo-1,6-dihydropyridazin-3-ylamino)phenyl]-4-(3-nitrophenyl)-1,2-dihydropyridine-3-carbonitrile (8b). The title compound was prepared from the reaction of **7** with 3-nitrobenzaldehyde, ethyl cyanoacetate, and ammonium acetate in 45% yield. Mp > 300 °C; ^{1}H NMR(DMSO-d_6) δ 6.65 (m, 1H, aromatic H), 6.84–6.87 (d, 1H, J = 9.7 Hz, CH pyridazine), 7.20–7.23 (d, 1H, J = 9.7 Hz, CH pyridazine), 7.37–7.43 (m, 2H, aromatic H), 7.67–7.70 (s 1H and d, 2H, J = 9, aromatic H), 7.77–7.80 (d, 2H, J = 9 Hz, aromatic H), 7.95 (s, 1H, aromatic H), 9.16 (s, 1H, NH, D_2O exchangeable), 12.11 (s, 1H, NH, pyridazine D_2O exchangeable), 12.87 (s, 1H, NH, pyridone, D_2O exchangeable); IR(KBr) cm^{-1}: 3400, 3300 (NH), 2200 (CN), 1680, 1660 (2C═O); MS *m*/*z*: 424 (M−2)$^+$.

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