A Simple, Convenient, One-Pot Synthesis of Dihydro-azolopyrimidines, DFT Calculation, and NMR Determination by Using H-Ferrierite Zeolite as Catalyst

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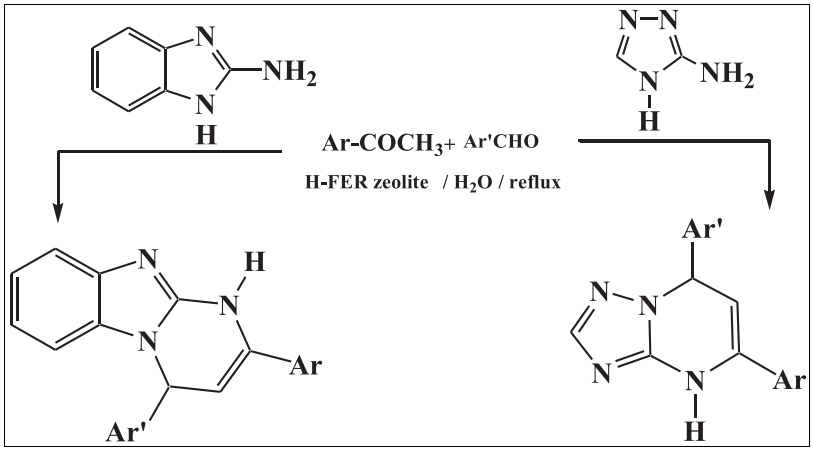

The multicomponent reaction of acetophenone derivatives with heterocyclic amines and benzaldehyde derivatives in water in the presence of H-ferrierite zeolite for short time 8–15 min afforded new series of [1,2,4]triazolo[1,5-*a*]pyrimidines and pyrimido[1,2-*a*]benzimidazole derivatives. The structure of the actual tutomeric product was established on the bases of spectral data [IR, NMR (^{1}H and ^{13}C), and nuclear Overhauser effect] and density functional theory calculations.

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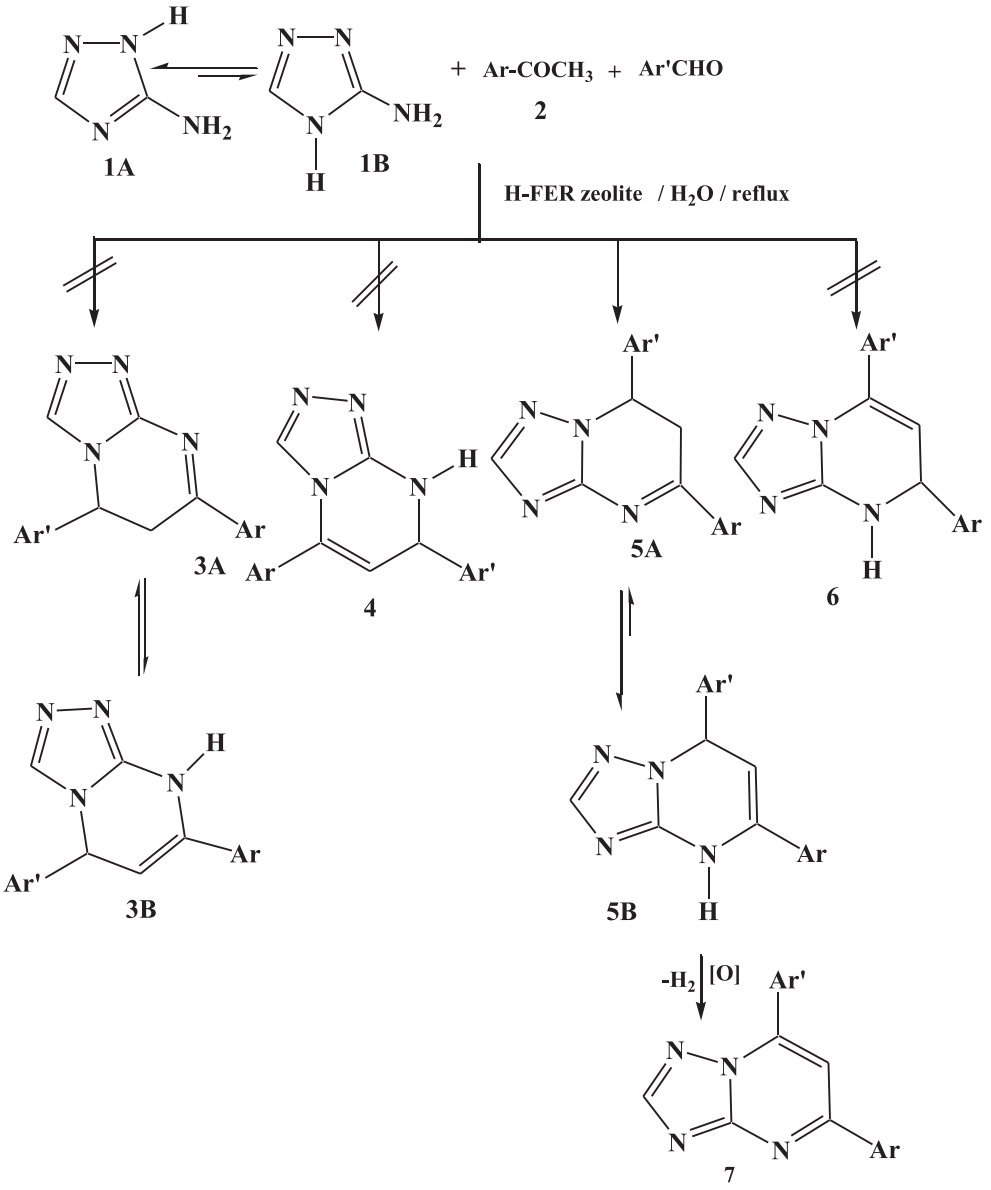
INTRODUCTION

Multicomponent reactions (MCRs) have been proven to be a very important and rapid way to access heterocyclic ring compounds in a single synthetic operation from simple building blocks and show high selectivity [1–3]. There remains the necessity to develop a more effective and convenient synthetic procedure as the reported methods have many disadvantages such as the use of a high-boiling solvent [e.g., dimethylformamide (DMF)] that is difficult to recover, excess amounts of acid or base, special apparatus, corrosive (e.g., HCl gas and trifluoroacetic acid) and hazardous (e.g., pyridine and piperidine,) reagents/solvents and special efforts to prepare the catalysts and adsorb the reactants on a solid support. RE exchanged Y zeolites are reported as effective catalyst in organic chemistry, petroleum industry, agriculture, and domestic water treatment, and their specificity in gas phase transformations is widely used in such industry [4]. Many organic reactions such as cyclization, alkylation, polymerization [5], or preparation of nitroalkane [6] occurred in gas phase or with reactants adsorbed within zeolite. Lately, there have been sundry reports on the utilization of acidic zeolites (HY) in macro-lactonization [7,8], acetylation [9], and *gem*-diacetalization [10], as well as in the synthesis and application of the organic-functionalized zeolite beta [11]. Many reports [12] indicated that 1,4-dihyd ro-azolopyrimidine were synthesized via cyclocondensation of amino azoles with α,β-unsaturated ketones (chalcones) [12,13] in DMF under reflux for 2–35 h. But this reaction has disadvantages such as isolation of mixture of products [14]. In addition, azolopyrimidine systems showed many pharmacological activities [15–17]. Among all of the aforementioned findings and as a part of our program that aimed at achieving simple and environmentally compatible synthetic methodologies in search of important heterocycles [18–20], we are interested in the synthesis of a new series of 1,4-di hydro-azolopyrimidine derivatives through MCR of heterocyclic amine, acetophenone derivatives, and substituted benzaldehydes by using catalytic amount of zeolite ferrierite, in its acidic form H-ferrierite (H-FER), in water. Moreover, we conducted an investigation of the actual tutomeric structure of the product through IR, NMR (^{1}H and ^{13}C), nuclear Overhauser effect (NOE), and density functional theory (DFT) calculations.

RESULTS AND DISCUSSION

Multicomponent reaction of 3-amino-1,2,4-triazole **1** with substituted benzaldehyde derivatives and acetophenone

Scheme 1



Ar / Ar': a, 4-FC_6H_4 / 4-FC_6H_4; b, 4-BrC_6H_4 / 4-FC_6H_4; c, 4-MeC_6H_4 / 4-FC_6H_4 ; d, 4-$MeOC_6H_4$ / 4-FC_6H_4; e, 4-FC_6H_4 / 3,4-$MeOC_6H_3$; f, 4-FC_6H_4 / 3,4,5-$MeOC_6H_2$

Table 1

Synthesis of 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines (**5a–f**) by using H-FER zeolite.

Entry	Ar/Ar′	Product	Time (min)	Yield (%)
1	4-FC_6H_4/4-FC_6H_4	**5a**	9.0	85
2	4-BrC_6H_4/4-FC_6H_4	**5b**	10.0	85
3	4-MeC_6H_4/4-FC_6H_4	**5c**	8.0	88
4	4-$MeOC_6H_4$/4-FC_6H_4	**5d**	8.0	87
5	4-FC_6H_4/3,4-$MeOC_6H_3$	**5e**	10.0	81
6	4-FC_6H_4/3,4,5-$MeOC_6H_2$	**5f**	9.0	80

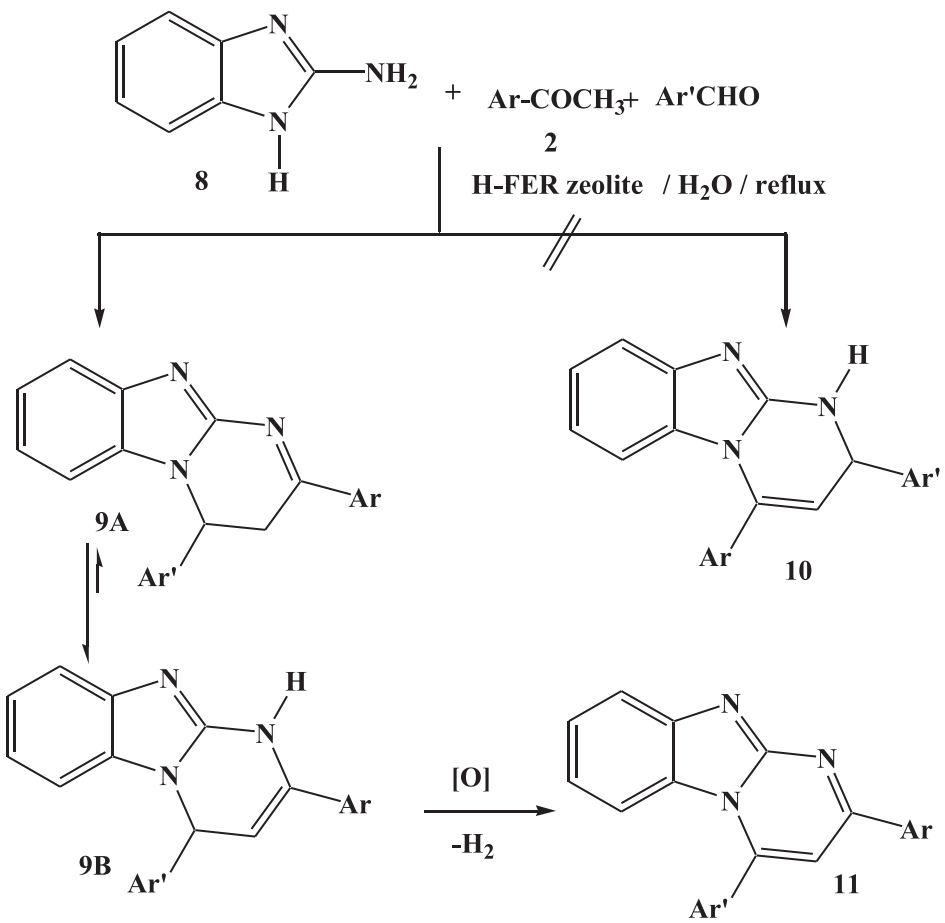
derivatives **2** were examined. When such reactions were carried out in refluxing water in the presence of 2 g of H-FER zeolite for 8–15 min, they yielded, in each case, one product (as evidenced by thin-layer chromatography) of the six isomers, **3A**, **3B**, **4**, **5A**, **5B**, and **6** (Scheme 1). All spectral data of the products are consistent with structure of **5B** rather than that of the other isomers, **3A**, **3B**, **4**, **5A**, and **6** (Scheme 1). For example, the IR spectra of the products revealed strong absorption bands for the NH–C=C– fragment in the region 1612–1658 cm^{-1}[14]. In ^1H NMR, the protons of the NH group, the aromatic

nuclei, and the dihydropyrimidine ring always appear, and these eliminate **3A**, **4**, **5A**, and **6**. Moreover, NOE difference experiments indicated that triazole proton and protons of aromatic substituent (Ar′) and proton of C_7-H do not show mutual signal in triazolo[1,5-*a*]pyrimidine ring, which is consistent with the structure of **5B**. All the triazolo[1,5-*a*]pyrimidine derivatives were obtained in excellent yields with good purity and in very short time (Table 1).

In order to explore the generality of the reaction, we extended our study using 2-aminobenzimidazole **8** as amino source, reacting with acetophenone derivatives **2**, H-FER zeolite as catalyst in presence of water with different substituted benzaldehydes to prepare a series of pyrimidobenzimidazole derivatives. The isolated product may be formulated as **9A**, **9B**, or **10** (Scheme 2, Table 2). The structure of **9B** could be readily established for this product based on IR and NMR (^{1}H and ^{13}C) spectra as well as on results of NOE difference experiments. Thus, the irradiation at the NH group resonance has not enhanced the C_4-H signal in the pyrimido[1,2-*a*]benzimidazole ring, which is consistent with the structure of **9B** (see Experimental part). Thus, the presence or absence of a NOE between specific protons allowed the structures for these compounds to be established.

This can suggest that the acid sites on zeolite work as active sites for this reaction and accelerate the reactions. We have proposed the plausible mechanism for the formation of [1,2,4]triazolo[1,5-*a*]pyrimidines **5a–f** or pyrimido[1,2-*a*]benzimidazole derivatives **9a–f** in the presence of H-FER zeolite (Scheme 3). The hypothesis supported the fact that initially the reaction was initiated by H-FER zeolite, which reacts with benzaldehydes and forms a complex **I**. Then complex **I** reacts with acetophenone derivatives to give the intermediate **II**. The latter intermediate **II** reacts with, for example, 3-amino-[1,2,4]triazole, giving

Scheme 2



Ar / Ar': a, 4-FC$_6$H$_4$ / 4-FC$_6$H$_4$; b, 4-BrC$_6$H$_4$ / 4-FC$_6$H$_4$; c, 4-MeC$_6$H$_4$ / 4-FC$_6$H$_4$; d, 4-MeOC$_6$H$_4$ / 4-FC$_6$H$_4$; e, 4-FC$_6$H$_4$ / 3,4-MeOC$_6$H$_3$; f, 4-FC$_6$H$_4$ / 3,4,5-MeOC$_6$H$_2$

Table 2

Synthesis of 1,4-dihydro-pyrimido[1,2-*a*]benzimidazole (**9a–f**) by using H-FER zeolite.

Entry	Ar/Ar′	Product	Time (min)	Yield (%)
1	4-FC_6H_4/4-FC_6H_4	**9a**	10.0	87
2	4-BrC_6H_4/4-FC_6H_4	**9b**	10.0	88
3	4-MeC_6H_4/4-FC_6H_4	**9c**	12.0	90
4	4-$MeOC_6H_4$/4-FC_6H_4	**5d**	13.0	90
5	4-FC_6H_4/3,4-$MeOC_6H_3$	**9e**	15.0	81
6	4-FC_6H_4/3,4,5-$MeOC_6H_2$	**9f**	15.0	80

rise to complex **III** and, upon loss of two water molecules, gives the target products **5B** (Scheme 3).

Molecular orbital calculations. The results of molecular orbital (MO) calculations using B3LYP/6-31G* [21] for compounds **1A**, **1B**, **3A**, **3B**, **5A**, **5B**, **6**, **9A**, **9B**, and **10** are depicted in Tables 3 and 4. 3-Amino-1,2,4-triazole is considered to exist in two forms, **1A** and **1B** (Scheme 1). Inspection of data in Table 3 revealed the following: the 3-amino-1,2,4-triazole **1A** form is more stable than **1B** by about 7.6 kcal and seemed to be the predominant form in the gas phase. The energy gap ($E_{LUMO} - E_{HOMO}$) of **1A** is less than that of **1B** by 13.5 kcal. As the energy gap decreases, the reactivity of compound increases; this means that compound **1A** is more reactive than compound **1B** in the reaction mechanism. The computed dipole moment that measures the polarity of compound showed that **1B** is more polar than **1A** by about 1.5 D. Therefore, compound **1B** is stabilized in aprotic solvent, whereas **1A** is stabilized in protic solvent. Also, the data predicted that **3B** is more stable than **3A** by about 4 kcal, that is, a statistical mixture of **3A** and **3B** is formed in the reaction medium, and **3B** is the predominant structure. The formation of **4** could be ruled out because it is less stable than **3A** by about 10 kcal. The products' reactivity, measured by the energy gap ($E_{LUMO} - E_{HOMO}$), indicated that **3B** is more reactive than **3A** by about 4 kcal (Table 3). For the MO calculations, a statistical mixture of **5A** and **5B** is formed where **5B** is more stable than **5A** by 2.2 kcal. Moreover, the energy gap ($E_{LUMO} - E_{HOMO}$) of **5B** is less than that of **5A** by about 10 kcal; this means that **5B** is more reactive than **5A**. In addition, compound **6** was ruled out because it was shown to be energetically less stable than **5A** and **5B** by 5.6 and 7.5 kcal, respectively. In summary, compound **5B** is energetically more stable than **3A**, **3B**, **4**, **5A**, or **6**, and it seemed to be the predominant isomer in the gas phase as

Scheme 3

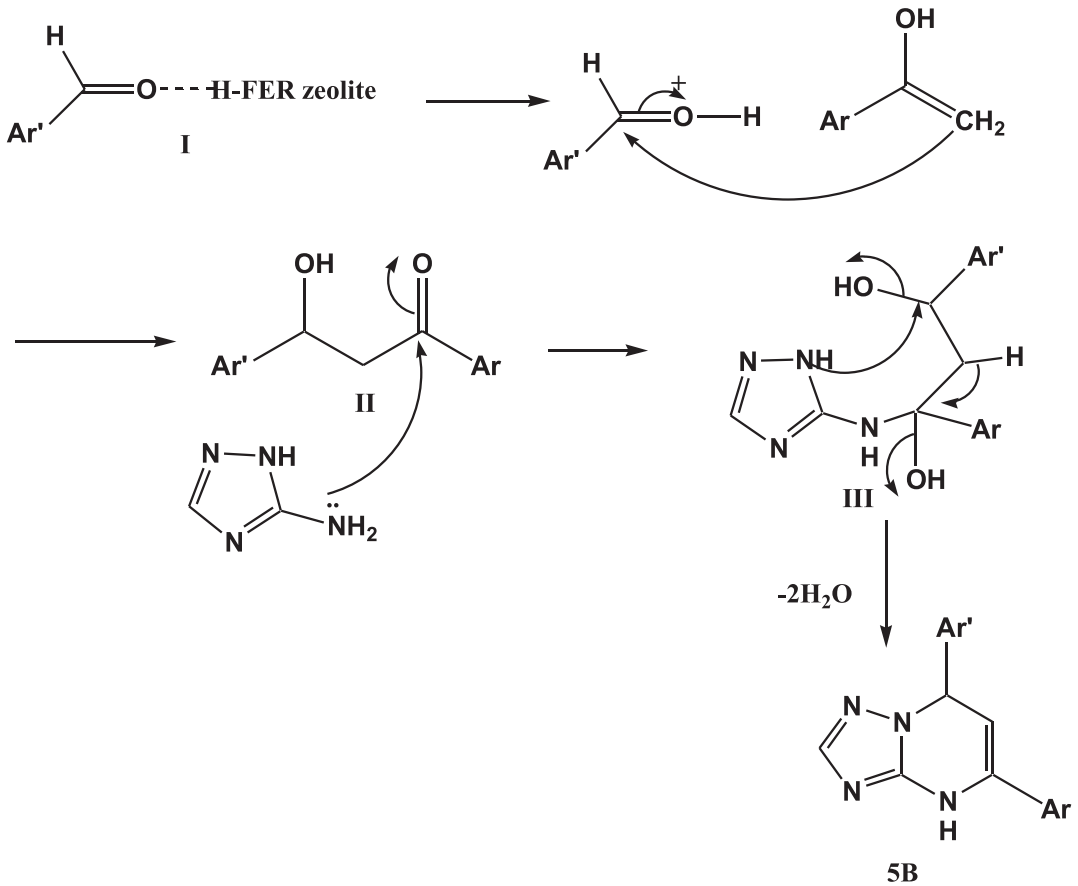


Table 3

Total energy (a.u.), energy of HOMO (a.u.), energy of LUMO (a.u.), energy gap (eV), and dipole moment (D) for compounds **1** and **3–6.**

Parameter	1A	1B	3A	3B	4	5A	5B	6
E_T, a.u.	−297.6188	−297.6005	−875.2154	−875.2217	−875.2059	−875.2292	−875.2327	−875.2202
E_{HOMO}, a.u.	−0.2171	−0.2274	−0.1989	0.2187	−0.1977	−0.2041	−0.2241	−0.2053
E_{LUMO}, a.u.	0.0171	0.0279	−0.0349	−0.0683	−0.0466	−0.0374	−0.0739	−0.0431
ΔE, eV	6.372	6.948	4.460	4.090	4.109	4.530	4.080	4.410
Dipole moment μ, D	3.909	5.426	6.193	8.117	6.4808	4.072	5.254	3.649

HOMO, highest occupied molecular orbital; LOMO, lowest unoccupied molecular orbital.

Table 4

Total energy (a.u.), energy of HOMO (a.u.), energy of LUMO (a.u.), energy gap (eV), and dipole moment (D) for compounds **9A**, **9B**, and **10.**

Parameter	9A	9B	10
E_T, a.u.	−1012.8308	−1012.8503	−1012.8203
E_{HOMO}, a.u.	−0.1911	−0.2057	0.1909
E_{LUMO}, a.u.	0.0342	0.0704	−0.0360
ΔE, eV	4.267	3.678	4.213
Dipole moment μ, D	5.231	4.245	4.185

HOMO, highest occupied molecular orbital; LOMO, lowest unoccupied molecular orbital.

indicated from ^{1}H and ^{13}C NMR in liquid phase. Also, the MO calculation predicted that the **9B** that formed in the reaction medium was fully optimized at the B3LYP/6-31G* level (Table 4), and the calculation indicated that **9B** was more stable than isomers **9A** and **10** by 12.2 and 18.9 kcal, respectively. Also, the reactivity of **9B** was greater than that of **9A** by 13.6 kcal and that of **10** by 12.3 kcal.

Because of the wide range of pharmacological activity of the oxidized form of [1,2,4]triazolo[1,5-*a*]pyrimidines and pyrimido[1,2-*a*]benzimidazoles [15–17], we cyclized compounds **5B** and **9B** with bromine in acetic acid to **7** and **11**, respectively (Schemes 1 and 2). The structure of compounds **7** and **11** was confirmed on the bases of spectral data and elemental analyses (see Experimental part).

CONCLUSIONS

In this context, we have developed an efficient and facile method for the synthesis of new series of [1,2,4]triazolo [1,5-*a*]pyrimidines and pyrimido[1,2-*a*]benzimidazoles by MCR using H-FER zeolite catalysts in water. The mild reaction conditions are reduced pollution, reusability, high selectivity, low cost, and short reaction time. Also, the structure of these products was established on the bases of spectral data [IR, NMR (^{1}H and ^{13}C), and NOE] and DFT calculations.

EXPERIMENTAL

Melting points were determined on an electrothermal Gallenkamp apparatus and are uncorrected. The IR spectra were recorded in KBr using a PyeUnicam SP-1000 spectrophotometer (Pye-Unicam, Ltd., Cambridge, UK). ^{1}H NMR spectra were obtained on a Varian EM-300 MHz spectrometer (^{1}H NMR 300 MHz) using DMSO-d_6, solvent with TMS as internal standard. ^{13}C NMR spectra were measured on a Varian EM-300MHz spectrometer (75 MHz). Mass spectra were recorded on an AEI MS 30 mass spectrometer operating at 70 eV. Elemental analyses were carried out by the Microanalytical Center of Cairo University, Giza, Egypt.

Reaction of acetophenone derivatives 2a–d with heterocyclic amines and benzaldehydes. A mixture of 3-amino-1,2,4-triazole **1** or benzimidazole **8** (1.0 mmol), benzaldehyde derivatives (1.0 mmol), acetophenone derivatives **2** (1.0 mmol), and water (5 mL) was taken in a round-bottom flask, H-FER zeolite (10 mol%) was added, and the mixture was stirred at 80 °C for 10–15 min. After completion of the reaction, as monitored by thin-layer chromatography, the zeolite catalyst was filtered first, and the reaction mass was cooled to room temperature; and the solid separated was filtered and washed with water, dried, and crystallized from the proper solvent to afford the corresponding 1,2,4-triazolo[1,5-*a*] pyrimidines **5a–f** or pyrimido[1,2-*a*]benzimidazole **9a–f** .

5,7-Di-(4-fluorophenyl)-4,7-dihydro-1,2,4-triazolo[1,5-a] pyrimidine (5a). Yellow solid, mp 180–182 °C (ethanol). ^{1}H NMR (DMSO-d_6) δ 5.20 (d, J = 4 Hz, 1H, CH), 6.12 (d, J = 4 Hz, 1H, CH), 7.09–7.75 (m, 8H, Ar-H), 8.23 (s, 1H, triazole-H), 10.11 (s, 1H, NH); IR (KBr) ν_{max} 3250, 1612 cm^{-1}. MS *m/z* (%) 312 (M^+ +2, 34), 311 (M^+ +1, 96), 310 (M^+, 100), 118 (43), 106 (12), 91 (40), 77 (72). *Anal*. Calcd for $C_{17}H_{12}F_2N_4$ (310.31): C, 65.80; H, 3.90; N, 18.06. Found: C, 65.74; H, 3.98; N, 18.15%.

5-(4-Bromophenyl)-7-(4-fluorophenyl)-4,7-dihydro-1,2,4-tria zolo[1,5-a]pyrimidine (5b). Yellow solid, mp 220–222 °C (DMF). ^{1}H NMR (DMSO-d_6) δ 5.23 (d, J = 3.6 Hz, 1H, CH), 6.24 (d, J = 3.6 Hz, 1H, CH), 7.17–7.83 (m, 8H, ArH), 8.74 (s, 1H, triazole-H), 10.09 (s, 1H, NH); IR (KBr) ν_{max} 3200, 1624 cm^{-1}. MS *m/z* (%) 373 (M^+ +2, 11), 372 (M^+ +1, 5), 371 (M^+, 58), 155 (15), 106 (32), 91 (67), 76 (100). *Anal*. Calcd for $C_{17}H_{12}BrFN_4$ (371.21): C, 55.01; H, 3.26; N, 15.09. Found: C, 55.23; H, 3.09; N, 15.01%.

7-(4-Fluoophenyl)-5-(4-methylphenyl)-4,7-dihydro-1,2,4-tria zolo[1,5-a]pyrimidine (5c). Orange solid, mp 199–201 °C (DMF). ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3H, CH_3), 5.14 (d, J = 3.6 Hz, 1H, CH), 6.23 (d, J = 3.6 Hz, 1H, CH), 7.17–7.53 (m, 8H, Ar-H), 7.66 (s, 1H, triazole-H), 10.03 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 20.96, 58.81, 95.99, 106.45, 115.25, 125.71, 128.74, 128.95, 131.24, 135.21, 138.28, 138.31, 149.36, 149.69. IR (KBr) ν_{max} 3310, 1626 cm^{-1}. MS *m/z* (%) 308 (M^+ +2, 1), 307 (M^+ +1, 7), 306 (M^+, 37), 305 (45), 211 (100), 118 (11), 91 (11). *Anal*. Calcd for $C_{18}H_{15}FN_4$ (306.13): C, 70.57; H, 4.94; N, 18.29. Found: C, 70.31; H, 4.69; N, 18.10%.

7-(4-Fluorophenyl)-5-(4-methoxyphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine (5d). Pale yellow solid, mp 230–232 °C (DMF). ^{1}H NMR (DMSO-d_6) δ 3.79 (s, 3H, OCH_3), 5.10 (d, J = 4 Hz, 1H, CH), 6.22 (d, J = 4 Hz, 1H, CH), 7.17–7.53 (m, 8H, Ar-H), 7.64 (s, 1H, triazole-H), 9.95 (s, 1H, NH); IR (KBr) ν_{max} 3195, 1632 cm^{-1}. MS *m/z* (%) 324 (M^+ +2, 6), 323 (M^+ +1, 11), 322 (M^+, 19), 118 (45), 91 (18). *Anal*. Calcd for $C_{18}H_{15}FN_4O$ (322.34): C, 67.07; H, 4.69; N, 17.38. Found: C, 66.92; H, 4.44; N, 17.21%.

5-(4-Fluorophenyl)-7-(3,4-dimethoxyphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine (5e). Yellow solid, mp 72–74 °C (ethanol). ^{1}H NMR (DMSO-d_6) δ 3.72, 3.82 (2 s, 6H, $2OCH_3$), 5.15 (d, J = 3.2 Hz, 1H, CH), 6.14 (d, J = 3.2 Hz, 1H, CH), 6.91 (d, J = 8 Hz, 1H, Ar-H), 7.0 (d, J = 8 Hz, 1H, Ar-H), 7.32 (d, J = 8 Hz, 2H, Ar-H), 7.55 (s, 1H, Ar-H), 7.67 (d, J = 8 Hz, 2H, Ar-H), 7.93 (s, 1H, triazole-H), 10.0 (s, 1H, NH); IR (KBr) ν_{max} 3194, 1658 cm^{-1}. MS *m/z* (%) 353 (M^+ +1, 22), 352 (M^+, 91), 324 (24), 257 (21), 215 (100), 173 (16), 138 (23), 121 (21), 91 (13), 77 (25). *Anal*. Calcd for $C_{19}H_{17}FN_4O_2$ (352.37): C, 64.76; H, 4.86; N, 15.90. Found: C, 64.56; H, 4.70; N, 15.82%.

5-(4-Fluorophenyl)-7-(3,4,5-trimethoxyphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine (5f). Orange solid, mp 132–134 °C (ethanol). ^{1}H NMR (DMSO-d_6) δ 3.75, 3.80, 3.87 (3 s, 9H, $3OCH_3$), 5.23 (d, J = 3.4 Hz, 1H, CH), 6.26 (d, J = 3.4 Hz, 1H, CH), 6.89 (d, J = 8 Hz, 2H, Ar-H), 7.18 (d, J = 8 Hz, 2H, Ar-H), 7.41 (s, 2H, Ar-H), 7.99 (s, 1H, triazole-H), 10.18 (s, 1H, NH); IR (KBr) ν_{max} 3311, 1615 cm^{-1}. MS *m/z* (%) 484 (M^+ +2, 10), 483 (M^+ +1, 15), 482 (M^+, 37), 105 (100), 91 (24), 76 (38). *Anal*. Calcd for $C_{20}H_{19}FN_4O_3$ (382.40): C, 62.82; H, 5.01; N, 14.65. Found: C, 62.65; H, 5.14; N, 14.49%.

2,4-Di-(4-fluorophenyl)-1,4-dihydro-pyrimido[1,2-a]benzimidazole (9a). Orange solid, mp 250–252°C (ethanol/dioxane). ^{1}H NMR (DMSO-d_6) δ 5.24 (d, J = 3 Hz, 1H, CH), 6.37 (d, J = 3 Hz, 1H, CH), 6.86–7.71 (m, 12H, ArH), 10.21 (s, 1H, NH); IR (KBr) ν_{max} 3301, 1640 cm^{-1}. MS *m/z* (%) 361 (M^+ +2, 2), 360 (M^+ +1, 10), 359 (M^+, 50), 358 (28), 357 (30), 264 (100), 90 (13). *Anal*. Calcd for $C_{22}H_{15}F_2N_3$ (359.38): C, 73.53; H, 4.21; N, 11.69. Found: C, 73.28; H, 4.06; N, 11.52%.

2-(4-Bromophenyl)-4-(4-fluorophenyl)-1,4-dihydro-pyrimido[1,2-a]benzimidazole (9b). Dark yellow solid, mp 260–262 °C (DMF). ^{1}H NMR (DMSO-d_6) δ 5.27 (d, J = 3.6 Hz, 1H, CH), 6.34 (d, J = 3.6 Hz, 1H, CH), 6.85–8.32 (m, 12H, Ar-H), 10.20 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 55.86, 97.81, 109.42, 114.31, 115.93, 119.37, 121.44, 127.04, 127.97, 128.16, 131.24, 131.76, 133.64, 137.87, 142.26, 147.87, 148.84, 151.25. IR (KBr) ν_{max} 3305, 1663 cm^{-1}. MS *m/z* (%) 422 (M^+ +2, 6), 421 (M^+ +1, 10), 420 (M^+, 45), 419 (100), 338 (10), 324 (47), 244 (10), 90 (6). *Anal*. Calcd for $C_{22}H_{15}BrFN_3$ (420.29): C, 62.87; H, 3.60; N, 10.00. Found: C, 62.66; H, 3.51; N, 10.12%.

4-(4-Fluorophenyl)-2-(4-methylphenyl)-1,4-dihydro-pyrimido[1,2-a]benzimidazole (9c). Orange solid, mp 270–272 °C (DMF). ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3H, CH_3), 5.21 (d, J = 4 Hz, 1H, CH), 6.35 (d, J = 4 Hz, 1H, CH), 6.85–7.55 (m, 12H, Ar-H), 10.21 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 20.70, 55.85, 96.57, 109.39, 114.22, 115.43, 116.22, 120.54, 121.99, 125.72, 126.56, 127.99, 128.55, 131.35, 134.01, 142.42, 142.65, 148.07, 151.15. IR (KBr) ν_{max} 3150, 1648 cm^{-1}. MS *m/z* (%) 357 (M^+ +2, 5), 356 (M^+ +1, 15), 355 (M^+, 70), 260 (100), 223 (6), 91 (6). *Anal*. Calcd for $C_{23}H_{18}FN_3$ (355.41): C, 77.73; H, 5.10; N, 11.82. Found: C, 77.56; H, 5.31; N, 11.62%.

4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-1,4-dihydro-pyrimido[1,2-a]bezimidazole (9d). Dark yellow solid, mp 240–242 °C (DMF). ^{1}H NMR (DMSO-d_6) δ 3.79 (s, 3H, OCH_3), 5.60 (d, J = 4 Hz, 1H, CH), 6.16 (d, J = 4 Hz, 1H, CH), 6.85–8.41 (m, 12H, Ar-H), 10.01 (s, 1H, NH); IR (KBr) ν_{max} 3100, 1638 cm^{-1}. MS *m/z* (%) 373 (M^+ +2, 14), 372 (M^+ +1, 25), 371 (M^+, 39), 369 (100), 326 (12), 276 (11), 148 (8). *Anal*. Calcd for $C_{23}H_{18}FN_3O$ (371.42): C, 74.38; H, 4.88; N, 11.31. Found: C, 74.20; H, 4.64; N, 11.09%.

2-(4-Fluorophenyl)-4-(3,4-dimethoxyphenyl)-1,4-dihydro-pyrimido[1,2-a]benzimidazole (9e). Orange solid, mp 220–222°C (ethanol). ^{1}H NMR (DMSO-d_6) δ 3.69, 3.72 (2s, 6H, $2OCH_3$), 5.23 (d, J = 3.6 Hz, 1H, CH), 6.25 (d, J = 3.6 Hz, 1H, CH), 6.79–8.25 (m, 11H, Ar-H), 10.12 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 55.46, 55.51, 56.38, 97.77, 109.74, 110.41, 112.0, 115.29, 115.90, 118.75, 119.29, 121.38, 128.1, 130.33, 131.05, 133.35, 134.26, 142.41, 148.05, 148.38, 148.80, 161.13. IR (KBr) ν_{max} 3147, 1624 cm^{-1}. MS *m/z* (%) 402 (M^+ +1, 18), 401 (M^+, 54), 400 (51), 399 (37), 264 (100), 200 (11), 133 (12), 90 (12), 76 (8). *Anal*. Calcd for $C_{24}H_{20}FN_3O_2$ (401.44): C, 71.81; H, 5.02; N, 10.47. Found: C, 71.65; H, 5.14; N, 10.28%.

2-(4-Fluorophenyl)-4-(3,4,5-trimethoxyphenyl)-1,4-dihydro-pyrimido[1,2-a]benzimidazole (9f). Yellow solid, mp 202–204°C (ethanol). ^{1}H NMR (DMSO-d_6) δ 3.69, 3.78, 3.81 (3 s, 9H, $3OCH_3$), 5.25 (d, J = 3.6 Hz, 1H, CH), 5.87 (d, J = 3.6 Hz, 1H, CH), 6.55 (s, 2H, Ar-H), 6.68–8.49 (m, 8H, Ar-H), 10.18 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 55.88, 56.23, 56.83, 59.96, 97.41, 103.85, 107.20, 109.75, 115.29, 115.50, 115.96, 119.40, 121.48, 128.25, 130.26, 132.15, 137.01, 137.54, 142.39, 148.0, 153.18. IR (KBr) ν_{max} 3159, 1635 cm^{-1}. MS *m/z* (%) 433 (M^+ +2, 5), 432 (M^+ +1, 21), 431 (M^+, 74), 264 (100), 236 (15), 111 (12), 97 (27), 83 (33), 72 (42), 57 (46). *Anal*. Calcd for $C_{25}H_{22}FN_3O_3$ (431.47): C, 69.59; H, 5.14; N, 9.74. Found: C, 69.40; H, 5.02; N, 9.58%.

Oxidation of compounds 5a–f and **9a–f**. Bromine (0.052 g, 1 mmol) in acetic acid (5 mL) was added dropwise to a stirred solution of the appropriate compounds **5a–f** or **9a–f** (1 mmol of each) in acetic acid (10 mL) and sodium acetate (0.5 g). The reaction mixture was stirred overnight and then poured onto ice-cold water, and the solid that precipitated was filtered off, washed with sodium bicarbonate solution and then with water, dried, and crystallized from the appropriate solvent to give the respective compounds, **7a–f** or **11a–f**.

***5,7-Di-(4-fluorophenyl)-1,2,4-triazolo[1,5-a]*pyrimidine (7a).** Orange solid, mp 234–236 °C (ethanol). ^{1}H NMR (DMSO-d_6) δ 7.22–7.83 (m, 8H, Ar-H), 8.17 (s, 1H, pyrimidine-H), 8.27 (s, 1H, triazole-H); MS *m/z* (%) 310 (M^+ +2, 47), 309 (M^+ +1, 29), 308 (M^+, 100), 307 (95), 95 (28), 91 (64), 77 (39), 76 (57). *Anal*. Calcd for $C_{17}H_{10}F_2N_4$ (308.29): C, 66.23; H, 3.27; N, 18.17. Found: C, 66.15; H, 3.08; N, 18.07%.

5-(4-Bromophenyl)-7-(4-fluorophenyl)-1,2,4-triazolo[1,5-a]pyrimidine (7b). Yellow solid, mp 270–272 °C (DMF). ^{1}H NMR (DMSO-d_6) δ 7.50–7.82 and 8.35–8.42 (m, 8H, ArH), 8.19 (s, 1H, pyrimidine-H), 8.73 (s, 1H, triazole-H); ^{13}C NMR (DMSO-d_6) δ 106.58, 115.55, 115.77, 125.29, 126.22, 129.83, 131.99, 132.56, 135.29, 146.65, 155.73, 156.14, 159.45. MS *m/z* (%) 370 (M^+ +1, 92), 369 (M^+, 100), 368 (71), 343 (38), 342 (75), 131 (79), 116 (50), 84 (58), 76 (67). *Anal*. Calcd for $C_{17}H_{10}BrFN_4$ (369.20): C, 55.31; H, 2.73; N, 15.18. Found: C, 55.20; H, 2.85; N, 15.09%.

7-(4-Fluorophenyl)-5-(4-methylphenyl)-1,2,4-triazolo[1,5-a] pyrimidine (7c). Dark yellow solid, mp 220–222 °C (DMF). ^{1}H NMR (DMSO-d_6) δ 2.41 (s, 3H, CH_3), 7.37–7.82 and 8.31–8.40 (m, 8H, ArH), 8.18 (s, 1H, pyrimidine-H), 8.61 (s, 1H, triazole-H); MS *m/z* (%) 306 (M^+ +2, 32), 305 (M^+ +1, 21), 304 (M^+, 75), 211 (27), 118 (54), 94 (31), 91 (46), 76 (100). *Anal*. Calcd for $C_{18}H_{13}FN_4$ (304.11): C, 71.04; H, 4.31; N, 18.41. Found: C, 71.11; H, 4.20; N, 18.24%.

7-(4-Fluorophenyl)-5-(4-methoxyphenyl)-1,2,4-triazolo[1,5-a]pyrimidine (7d). Orange solid, mp 248–250 °C (DMF). ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 3H, OCH_3), 7.10–7.52 and 8.07–8.38 (m, 8H, Ar-H), 8.07 (s, 1H, pyrimidine-H), 8.65 (s, 1H, triazole-H); ^{13}C NMR (DMSO-d_6) δ 55.45, 106.11, 114.35, 115.52, 115.74, 126.40, 128.39, 129.59, 132.47, 132.56, 146.14, 155.78, 160.25, 161.98. MS *m/z* (%) 322 (M^+ +2, 6), 321 (M^+ +1, 15), 320 (M^+, 100), 292 (19), 90 (3), 76 (6). *Anal*. Calcd for $C_{18}H_{13}FN_4O$ (320.33): C, 67.49; H, 4.09; N, 17.49. Found: C, 67.23; H, 4.25; N, 17.19%.

5-(4-Fluorophenyl)-7-(3,4-dimethoxyphenyl)-1,2,4-triazolo [1,5-a]yrimidine (7e). Orange solid, mp 138–140 °C (ethanol). ^{1}H NMR (DMSO-d_6) δ 3.72, 3.87 (2s, 6H, $2OCH_3$), 7.25 (s, 2H, pyrimidine-hand triazole-H), 7.40–7.44 and 8.25–8.29 (m, 3H, Ar-H), 7.69 (d, J = 9 Hz, 2H, ArH), 7.89 (d, J = 9 Hz, 2H, ArH); MS *m/z* (%) 352 (M^+ +2, 15), 351 (M^+ +1, 11), 350 (M^+, 36), 349 (42),155 (13), 138 (56), 105 (15), 91 (24), 77 (100). *Anal*. Calcd for $C_{19}H_{15}FN_4O_2$ (350.36): C, 65.14; H, 4.32; N, 15.99. Found: C, 64.94; H, 4.24; N, 15.79%.

5-(4-Fluorophenyl)-7-(3,4,5-trimethoxyphenyl)-1,2,4-triazolo [1,5-a]pyrimidine (7f). Orange solid, mp 260–262 °C (ethanol/dioxane). ^{1}H NMR (DMSO-d_6) δ 3.39, 3.96 (2s, 9H, $3OCH_3$), 6.14 (d, J = 7 Hz, 2H, ArH), 6.82 (d, J = 7 Hz, 2H, ArH), 7.51, 8.37 (2s, 2H, Ar-H), 7.62 (s, 2H, pyrimidine-H and triazole-H); MS *m/z* (%) 382 (M^+ +2, 4), 381 (M^+ +1, 2), 380 (M^+, 12), 379 (19), 212 (42), 94 (26),76 (100). *Anal*. Calcd for $C_{20}H_{17}FN_4O_3$ (380.38): C, 63.15; H, 4.50; N, 14.73. Found: C, 63.0; H, 4.32; N, 14.50%.

2,4-Di-(4-fluorophenyl)-pyrimido[1,2-a]benzimidazole (11a). Orange solid, mp > 300 °C (dioxane). ^{1}H NMR (DMSO-d_6) δ 6.86–7.71 (m, 12H, ArH), 8.32 (s, 1H, pyrimidine-H); MS *m/z* (%) 359 (M^+ +2, 24), 358 (M^+ +1, 18), 357 (M^+, 58), 356 (48), 262 (26), 167 (10), 95 (32), 76 (100). *Anal*. Calcd for $C_{22}H_{13}F_2N_3$ (357.36): C, 73.94; H, 3.67; N, 11.76. Found: C, 73.68; H, 3.48; N, 11.55%.

2-(4-Bromophenyl)-4-(4-fluorophenyl)-pyrimido[1,2-a]benzi midazole (11b). Yellow solid, mp 300–302 °C (DMF). ^{1}H NMR (DMSO-d_6) δ 6.73–7.97 (m, 12H, Ar-H), 8.32 (s, 1H, pyrimidine-H); MS *m/z* (%) 420 (M^+ +2, 14), 419 (M^+ +1, 36), 418 (M^+, 100), 105 (25), 91 (20), 77 (37). *Anal*. Calcd for $C_{22}H_{13}BrFN_3$ (418.26): C, 63.17; H, 3.13; N, 10.05. Found: C, 63.0; H, 3.41; N, 10.22%.

4-(4-Fluorophenyl)-2-(4-methylphenyl)-pyrimido[1,2-a]benzi midazole (11c). Orange solid, mp 309–311 °C (DMFDMF). ^{1}H NMR (DMSO-d_6) δ 2.46 (s, 3H, CH_3), 6.72–7.95 (m, 12H, Ar-H), 8.36 (s, 1H, pyrimidine-H); MS *m/z* (%) 354 (M^+ +1, 26), 353 (M^+, 100), 352 (93), 351 (44), 177 (22), 176 (39), 162 (20), 106 (17), 91 (15), 77 (19). *Anal*. Calcd for $C_{23}H_{16}FN_3$ (353.39): C, 78.17; H, 4.56; N, 11.89. Found: C, 78.05; H, 4.29; N, 11.87%.

4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-pyrimido[1,2-a]ben zimidazole (11d). Yellow solid, mp 290–292 °C (DMF). ^{1}H NMR (DMSO-d_6) δ 3.93 (s, 3H, OCH_3), 6.67–7.93 (m, 12H, Ar-H), 8.29 (s, 1H, pyrimidine-H); MS *m/z* (%) 369 (M^+, 100), 368 (77), 342 (59), 341 (96), 220 (36), 169 (27), 133 (59), 105 (82), 90 (32), 77 (96). *Anal*. Calcd for $C_{23}H_{16}FN_3O$ (369.39): C, 74.78; H, 4.37; N, 11.38. Found: C, 74.65; H, 4.24; N, 11.18%.

2-(4-Fluorophenyl)-4-(3,4-dimethoxyphenyl)-pyrimido[1,2-a] benzidazole (11e). Dark orange solid, mp 288–290 °C (ethanol). ^{1}H NMR (DMSO-d_6) δ 3.66, 3.75 (2s, 6H, $2OCH_3$), 6.79–8.25 (m, 11H, Ar-H), 8.27 (s, 1H, pyrimidine-H); MS *m/z* (%) 401 (M^+ +2, 5), 400 (M^+ +1, 26), 399 (M^+, 38), 106 (45), 90 (25), 76 (58). *Anal*. Calcd for $C_{24}H_{18}FN_3O_2$ (399.14): C, 72.17; H, 4.54; N, 10.52. Found: C, 72.03; H, 4.34; N, 10.34%.

2-(4-Fluorophenyl)-4-(3,4,5-trimethoxyphenyl)-pyrimido [1,2-a]benzimidazole (11f). Orange solid, mp 236–2328 °C (ethanol/dioxane). ^{1}H NMR (DMSO-d_6) δ 3.72, 3.87 (2s, 9H, $3OCH_3$), 7.25 (s, 2H, Ar-H, pyrimidine-H), 7.42–7.44 and 8.27–8.27 (m, 5H, Ar-H), 7.73 (d, J = 9 Hz, 2H, Ar-H), 7.89 (d, J = 9 Hz, 2H, Ar-H); MS *m/z* (%) 431 (M^+ +2, 14), 430 (M^+ +1, 33), 429 (M^+, 100), 428 (78), 105 (16), 90 (10), 75 (14). *Anal*. Calcd for $C_{25}H_{20}FN_3O_3$ (429.44): C, 69.92; H, 4.42; N, 9.78. Found: C, 69.68; H, 4.20; N, 9.61%.

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