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Article

2-Methyl-7-Substituted Pyrazolo[1,5-*a*]pyrimidines: Highly Regioselective Synthesis and Bromination

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Este trabalho descreve a reação de ciclocondensação de 3-amino-5-metil-1*H*-pirazol com 1,1,1-tricloro-4-alcóxi-3-alquen-2-onas [$CCl_3C(O)CH=C(R^1)OR$, onde R^1/R = H/Me, Me/Et, Et/Me, Pr/Et, Bu/Me, *iso*-Bu/Me] e β-dimetilaminovinil cetonas [$R^2C(O)CH=CHNMe_2$, onde R^2 = Ph, Ph-4-Me, Ph-4-F, Ph-4-Cl, Ph-4-Br, Ph-4-NO_2, fur-2-il, tien-2-il, pirrol-2-il, pyrid-2-il], em refluxo de ácido acético para a obtenção de uma série de catorze pirazolo[1,5-*a*]pirimidinas. Os produtos foram obtidos em bons rendimentos (65-98%). Este trabalho apresenta ainda uma metodologia simples e seletiva para a obtenção de 3-bromo-pirazolo[1,5-a]pirimidinas, com rendimentos de 70-98%.

The reaction of 3-amino-5-methyl-1*H*-pyrazole with 1,1,1-trichloro-4-alkoxy-3-alken-2-ones [$CCl_3C(O)CH=C(R^1)OR$, where R^1/R = H/Me, Me/Et, Et/Me, Pr/Et, Bu/Me, *iso*-Bu/Me] or β-dimethylaminovinyl ketones [$R^2C(O)CH=CHNMe_2$, where R^2 = Ph, Ph-4-Me, Ph-4-F, Ph-4-Cl, Ph-4-Br, Ph-4-NO_2, fur-2-yl, thien-2-yl, pyrrol-2-yl, pyrid-2-yl], in acetic acid under reflux for 16 hours, furnished highly regioselective the halomethylated pyrazolo[1,5-*a*]pyrimidines and aryl[heteroaryl]pyrazolo[1,5-*a*]pyrimidines, respectively. A protocol for the bromination reaction at the 3-position pyrazolo[1,5-*a*]pyrimidines also was investigated.

Keywords: pyrimidines, pyrazoles, pyrazolo[1,5-*a*]pyrimidines, enones, bromination

Introduction

Among the broad range of templates, heterocycle scaffolds represent the most promising molecules as lead structures in the discovery of novel synthetic drugs[1] and the revision of synthetic methods for their obtainment are intense.[2] In particular, the pyrazolo[1,5-*a*]pyrimidine heterocyclic can be found in a large number of pharmaceutical agents with a diverse range of activities. Pyrazolo[1,5-*a*] pyrimidines are purine analogues and as such have useful properties as antimetabolites in purine biochemical reactions. Compounds of this class have attracted wide pharmaceutical interest because their antitrypanisommal activity,[3] antischistosomal activity,[4] activity as HMG-CoA reductase inhibitors,[5] COX-2 selective inhibitors,[6] AMP phosphodiesterase inhibtors,[7] KDR kinase inhibitors,[8] selective peripheral benzodiazepine receptor ligants[9] and as antianxiety agents.[10] Recently other pharmaceutical activity has been reported, for example, as an agent for the treatment of sleep disorders[11] and as an oncological agent.[12] The show examples highlight the high level of interest in variously substituted pyrazolo[1,5-*a*]pyrimidines and their modified analogues there is a wide range of methods available for the synthesis of pyrazolo[1,5-*a*]pyrimidines.[13] However, a facile procedure that can incorporate diversity structural it is high desirable. There are a limitedness number and variety of pyrazolo pyrimidines trifluoromethyl substituted described in literature.[14] Conversely, pyrazolo[1,5-*a*] pyrimidines trichloromethyl substituted are rare.[15] The most convenient method to construct trihalogenated compounds is to use halogen-containing building blocks as starting reagents.[16,17] Our research group developed a general procedure for preparing β-alkoxyvinyl trihalomethyl ketones by acylation of enol ethers and acetals using

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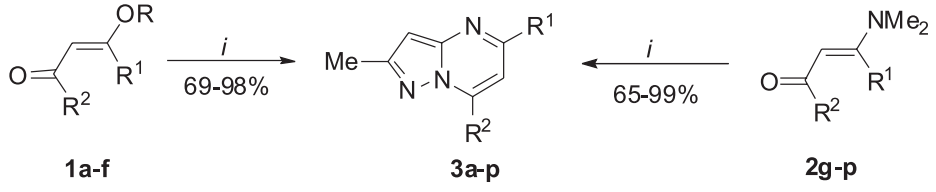
functionalized acyl groups CX_3CO (where X = F and Cl).[16] In addition, we have exhaustively studied the versatility of the β-alkoxyvinyl trihalomethyl ketones on heterocyclic synthesis and our research have resulting in outstanding contributions to heterocyclic synthesis.[2,16] On the other hand, aminopyrazoles are known to be highly reactive heterocyclic compounds, e.g., the nucleophilic attack of C-4 of the aminopyrazoles on the carbonyl groups,[18] and the N-nucleophilic attack on aromatic aldehydes yielding aldimines, have been extensively reported.[19] Aminopyrazoles also react as electron-rich dienophiles in the inverse electron demand Diels-Alder [4+2] cycloaddition reactions.[20] The use of 3- and 5-aminopyrazoles as precursors of fused heterocycles, such as pyrazolo[1,5-*a*]pyrimidines[21] and pyrazolo[3,4-*b*]pyridines[22] has also been described. Additionally, halogenation of pyrazolo[1,5-*a*]pyrimidines can be used to obtain key substructures in a large variety of compounds with important biological activities, and the halogenated compounds also can be used as reagents in cross-coupling reactions with terminal acetylenes, organotin aryl derivatives or aryl boronic acids.[23] Thus, in the course of our investigations on heterocyclic chemistry and in view of the growing importance of halogenated heterocycles, the aim of this study is to show: (*i*) the synthesis of halomethyl-containing pyrazolo[1,5-*a*] pyrimidines (**3**) from the reaction of 3-amino-5-methyl-1*H*-pyrazole with 4-alkoxy-1,1,1-trichloro-3-alken-2-ones (**1**) or β-dimethylaminovinyl ketones (**2**) (Scheme 1) and (*ii*) the bromination of the pyrazolo[1,5-*a*]pyrimidines (**3**) with bromine to obtain 3-bromopyrazolo[1,5-*a*]pyrimidines (**4**) (Scheme 2).

Results and Discussion

The 4-alkoxy-1,1,1-trichloro-3-alken-2-ones **1a**-**f**, were synthesized from the reaction of trichloroacetyl chloride with enol ether or acetal, in accordance with the methodology developed in our laboratory.[16] The β-dimethylaminovinyl ketones **2g**-**p** were prepared from the reaction of *N,N*-dimethylformamide dimethylacetal with methyl ketones, using the procedure described in the literature.[24] The 3-amino-5-methyl-1*H*-pyrazole used is commercially available.

The general methodology used in this work for preparing the halomethylated- (**3a**-**f**) and aryl-pyrazolo[1,5-*a*] pyrimidines (**3g**-**p**) was similar to the methodology described in the literature for the cyclocondensation reaction of a β-dicarbonyl compounds with 3-amino-pyrazole.[25] The reaction was carried out from the cyclocondensation reaction of the 3-amino-5-methyl-1*H*-pyrazole with 4-alkoxy-1,1,1-trichloro-3-alken-2-ones (**1a**-**f**), or β-dimethylaminovinyl ketones (**2g**-**p**), in reflux of acetic acid for 16 hours. The crude compounds **3** were purified by recrystallization from hexane, and the pure products were obtained in moderate to high yields (65-98%). The structure of compounds **3** was confirmed by $^1H/^{13}C$ NMR spectroscopy and mass



1a-f **3a-p** **2g-p**

i : 3-amino-5-methyl-1*H*-pyrazole, AcOH, reflux, 16h

Reagent	R	R^1	R^2	Product	Yield[a]
1a	Me	H	CCl_3	**3a**	87
1b	Et	Me	CCl_3	**3b**	75
1c	Me	Et	CCl_3	**3c**	80
1d	Et	Pr	CCl_3	**3d**	98
1e	Me	Bu	CCl_3	**3e**	69
1f	Me	*i*-Bu	CCl_3	**3f**	98

Reagent	R^1	R^2	Product	Yield[a]
2g	H	Ph	**3g**	92
2h	H	Ph-4-Me	**3h**	90
2i	H	Ph-4-F	**3i**	82
2j	H	Ph-4-Cl	**3j**	98
2k	H	Ph-4-Br	**3k**	99
2l	H	Ph-4-NO_2	**3l**	83
2m	H	Fur-2-yl	**3m**	65
2n	H	Thien-2-yl	**3n**	72
2o	H	Pyrrol-2-yl	**3o**	80
2p	H	Pyrid-2-yl	**3p**	76

[a]Yield of isolated product.

Scheme 1

spectrometry. For example, compound **3b** presented a ^{1}H NMR signal at 6.54 ppm that was assigned to the pyrazole C3–H, signal at 7.28 ppm assigned to the pyrimidine C6–H, and a doublet at 2.68 ppm corresponding to the pyrimidine C5–Me. The ^{13}C NMR chemical shift assignment of products was obtained with the help of HMBC (Heteronuclear Multiple Bond Correlation) two-dimensional correlation spectra. The HMBC spectrum showed a cross-peak between the signal at 7.28 ppm (pyrimidine C6–H) and at 157.5 ppm (pyrimidine C5). There was also a cross-peak between the ^{1}H NMR signal at 2.68 ppm (pyrimidine C5–Me) and the ^{13}C NMR signal at 157.5 ppm (pyrimidine C5) and another one between the ^{1}H NMR signal at 7.28 ppm (pyrimidine C6–H) and the ^{13}C NMR signal at 148.9 ppm (pyrimidine C6). This information is in agreement with the proposed structure, and this structure was confirmed by X-ray diffraction for compound **3g** (Figure 1).[26]

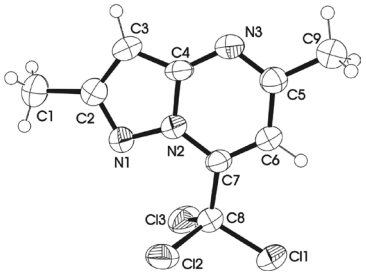


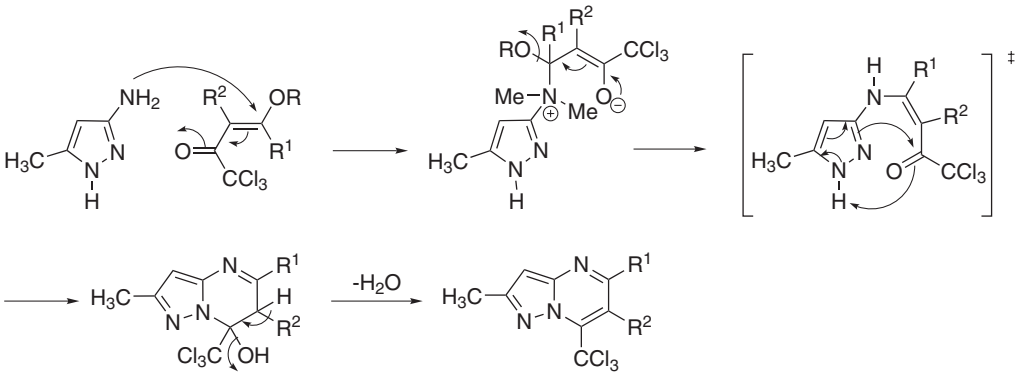
Figure 1. ORTEP of 2,5-dimethyl-7-trichloromethylpyrazolo[1,5-*a*] pyrimidine (**3b**).

A mechanism to reaction is suggest in Scheme 2, the reaction probably involved an initial C–N bond formation, from the attack of the nitrogen atom of the NH_2 group on the β-carbon of the enone **1**,**2**, with subsequent substitution of the alkoxy or *N,N*,-dimethylamino group, to furnish the enamino ketone intermediates. In a second moment, there was an intramolecular nucleophilic addition of the pyrazole ring nitrogen atom to the carbonyl carbon of the enone **1**,**2**, with subsequent elimination of one molecule of water.[27]

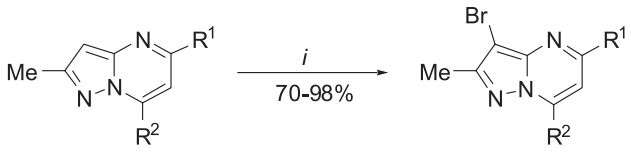
In contrast with previous studies,[28,29] the reaction was highly regioselective and only the pyrazolo[1,5-*a*] pyrimidine isomer was obtained, where R^2 was attached to C7 and R^1 was attached to C5 of the pyrimidine ring. The high regiosselectively of the reaction could be rationalized in terms of the difference of the nucleophilicity of the nitrogen atoms of the NH_2 group (soft) and N1/N2 of the pyrazole ring (hard), together with the difference of the electrophilicity of the β-carbon atom (soft) and carbonylic carbon (hard) of the enone **1,2**. In addition, semi-empirical quantum chemical calculations were used to compare the stability of the possible intermediates formed before the pyrimidine ring closure. The analyzes of the stability of these intermediates showed that the enaminone formed by the addition of the NH_2 group of the aminopyrazole on the C-β possesses the higher stability (>10 kcal mol^{-1}) than the enaminone formed by the addition of the nitrogen ring pyrazole on the C-β. For this study, the semi-empirical AM1 (Austin Model 1) method incorporated in the Hyperchem software[30,31] was implemented.

In a second step of this study, we reacted the pyrazolo[1,5-*a*]pyrimidines **3a**,**b**,**d**,**g**,**i**-**n** with bromine to obtain 3-bromopyrazolo[1,5-*a*]pyrimidines **4a**,**b**,**d**,**g**,**i**-**n** (Scheme 3). The 3-bromo-2-methyl-7-trichloro methylpyrazolo[1,5-*a*]pyrimidines **4a**,**b**,**d** and 3-bromo-2-methyl-7-arylpyrazolo[1,5-*a*]pyrimidine **4g**,**i**-**n** were synthesized by treating the pyrazolo[1,5-*a*] pyrimidines with *N*-bromosuccinimide in THF under reflux for 20 h. Crude compounds **4** were purified by recrystalization from hexane, and obtained in good yields (70-98%).

Considering the reaction conditions used for an electrophilic aromatic substitution, the selectivity of the bromination reaction of the pyrazolo[1,5-*a*]pyrimidines described in the present work can be understood from the resonance structures of the arenium-*like* intermediates (Scheme 4). When electrophilic bromine reacted in the C-3, four resonance structures of the intermediate were originated, whereas when the same eletrophile reacted in



Scheme 2



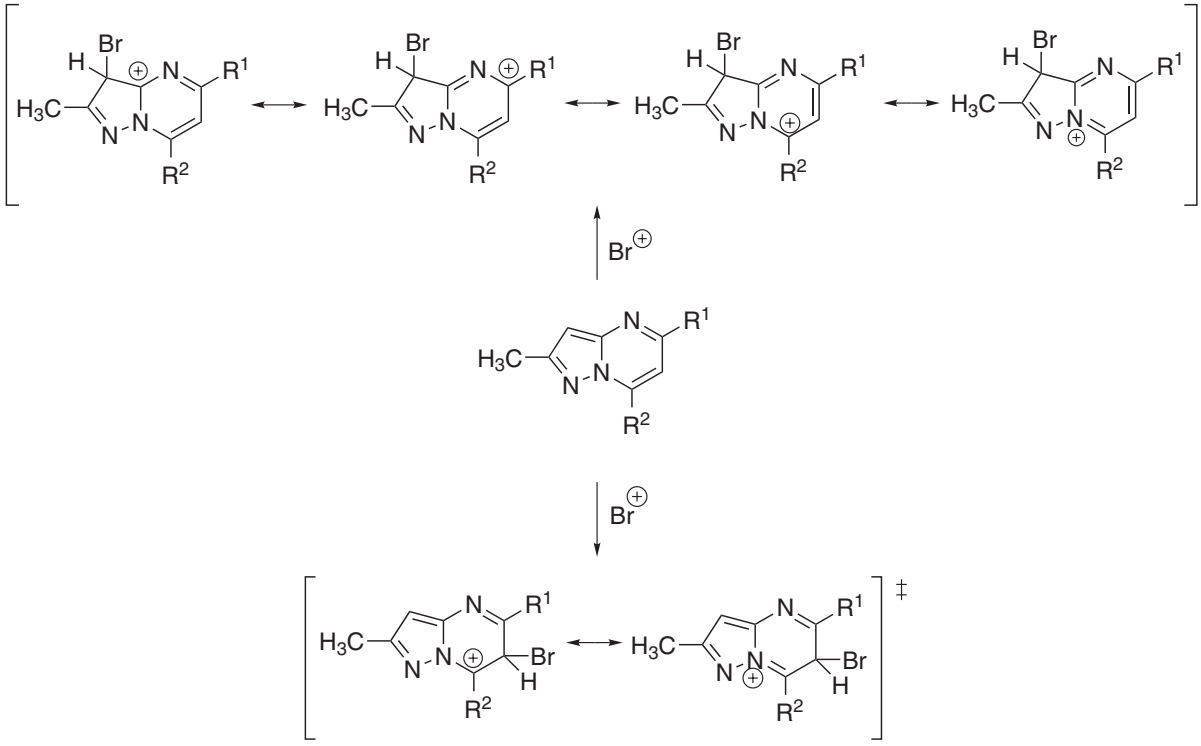
3 **4**

i : NBS, THF, reflux, 20h

Reagent	R^1	R^2	Product	Yield[a]	Reagent	R^1	R^2	Product	Yield[a]
3a	H	CCl_3	**4a**	89	**3j**	H	Ph-4-Cl	**4j**	95
3b	Me	CCl_3	**4b**	78	**3k**	H	Ph-4-Br	**4k**	98
3d	Pr	CCl_3	**4d**	88	**3l**	H	Ph-4-NO_2	**4l**	87
3g	H	Ph	**4g**	78	**3m**	H	Fur-2-yl	**4m**	70
3i	H	Ph-4-F	**4i**	95	**3n**	H	Thien-2-yl	**4n**	91

[a]Yield of isolated product.

Scheme 3



Scheme 4

C-6, only two resonance structures of the intermediate were generated. In addition, it is well-known that pyrazoles are π-exceeding rings and pyrimidines are π-deficient rings. Thus, the pyrazole ring, as expected, is more reactive than the pyridines in this bromination reaction.[32] Finally, although the reaction conditions could be used for side chain bromination reaction of methyl aromatics, such as pyridines and benzoderivatives,[33] in the case of methyl pyrazoles there are no reports in the literature about side chain bromination reactions.[23] Our results of the bromination reaction are in accordance with those described in the literature.

Conclusions

In summary, the synthesis described in this paper is a highly regioselective, practical and simple method for the preparation of halomethyl-containing pyrazolo[1,5-*a*] pyrimidines from 3-amino-5-methyl-1*H*-pyrazole and 1,3-dieletrophilic compounds. In addition, we reported a mild and convenient protocol for 3-halogenation of pyrazolo[1,5-*a*]pyrimidines with NBS and showed that the present procedure gave the products in good yields.

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Experimental

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. Yields listed in Schemes 1 and 2. All melting points were determined on a Reichert Thermovar apparatus. The $^{1}H/^{13}C$ NMR and 2D NMR spectra were recorded on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz and ^{13}C at 100.61 MHz) 298 K, digital resolution of ± 0.01 ppm, with 0.1 mol L^{-1} solution in $CDCl_3$ as solvent or Acetone-d_6 containing TMS as internal standard. All spectra were registred in a 5 mm tube, at a natural abundance. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split-splitless, injector, autosampler, cross-linked HP-5 capillary column (30 m 0.32 mm of internal diameter), and helium was used as the carrier gas.

*General procedure for the preparation of pyrazolo[1,5-a] pyrimidines **3a**-**p***

A solution of 3-amino-5-methyl-1*H*-pyrazole (1.0 mmol) in acetic acid (5 mL) was added to a stirred precursor **1** or **2** (1.0 mmol) in acetic acid (5 mL). The mixture was stirred for 16 h and after the reaction time, the products were extracted with chloroform (3 × 10 mL), washed with distiled water (3 × 10 mL) and dried on magnesium sulfate. The solvent was removed in a rotary evaporator and the products **3** were purified by recrystallization from hexane.

*General procedure for the preparation of 3-bromopyrazolo[1,5-a]pyrimidines **4a**,**b**,**d**,**g**,**i**-**n***

A mixture of pyrazolo[1,5-*a*]pyrimidine **3** (1.0 mmol), *N*-bromocuccinimide (1.0 mmol) and THF (5 mL) was stirred for 20 h under reflux temperature. After the reaction time, the solution was extracted with chloroform (3 × 10 mL), washed with distilled water (3 × 10 mL) and dried on magnesium sulfate. The solvent was removed in a rotary evaporator and the products **4** were purified by recrystallization from hexane.

*7-Trichloromethyl-2-methylpyrazolo[1,5-a]pyrimidine (**3a**)*

$C_8H_6Cl_3N_3$, solid, mp 94-96 °C; MW 250.52. ^{1}H NMR (400 MHz, $CDCl_3$): δ (J_{H-H}, Hz) 8.55 (d, 1H, H5, *J* 4.4), 7.43 (d, 1H, H6, *J* 4.4), 6.71 (s, 1H, H3), 2.58 (s, 3H, CH3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7 (C5), 156.5 (C2), 153.0 (C3a), 147.7 (C7), 109.4 (C6), 103.1 (C3), 94.4 (CCl_3), 20.5 (CH_3). MS *m/z* (%) 249 (M^+, 46), 214 (100), 144 (42), 50 (25). Anal. Calc.: C 38.36; H 2.41; N 16.77%. Found: C 38.30; H 2.56; N 16.63%.

*7-Trichloromethyl-2,5-dimethylpyrazolo[1,5-a]pyrimidine (**3b**)*

$C_9H_8Cl_3N_3$, solid, mp 118-120 °C; MW 264.54. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (s, 1H, H6), 6.54 (s, 1H, H3), 2.68 (s, 3H, H8), 2.58 (s, 3H, CH_3).^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5 (C5), 155.1 (C2), 150.6 (C3a), 141.9 (C7), 104.9 (C6), 96.2 (C3), 89.1 (CCl_3), 24.8 (C8), 14.9 (CH_3). MS *m/z* (%) 263 (M^+, 68), 228 (100), 158 (61), 107 (26) 73 (33). Anal. Calc.: C 40.86; H 3.05; N 15.88%. Found: C 40,67; H 3.09; N 15.83%.

*7-Trichloromethyl-5-ethyl-2-methylpyrazolo[1,5-a] pyrimidine (**3c**)*

$C_{10}H_{10}Cl_3N_3$, solid, mp 69-70 °C; MW 278.57. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (s, 1H, H6), 6.56 (s, 1H, H3), 2.93 (q, 2H, H8), 2.59 (s, 3H, CH_3), 1.40 (t, 2H, H9). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2 (C5), 154.8 (C2), 150.7 (C3a), 141.8 (C7), 103.9 (C6), 96.3 (C3), 89.1 (CCl_3), 31.5 (C8), 14.8 (CH_3), 12.6 (C9). MS *m/z* (%) 277 (M^+, 53), 242 (100), 207 (80), 51 (20). Anal. Calc.: C 43.12; H 3.62; N 15.08%. Found: C 42.80; H 3.63; N 14.80%.

*7-Trichloromethyl-2-methyl-5-propylpyrazolo[1,5-a] pyrimidine (**3d**)*

$C_{11}H_{12}Cl_3N_3$, MW 292.60, mp 59-61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (s, 1H, H6), 6.56 (s, 1H, H3), 2.88 (t, 2H, H8), 2.56 (s, 3H, CH_3), 1.85 (sext, 2H, H9), 1.04 (t, 3H, H10). ^{13}C NMR (100 MHz, $CDCl_3$,): δ 161.2 (C5), 154.9 (C2), 150.5 (C3a), 141.9 (C7), 104.2 (C6), 96.2 (C3), 89.1 (CCl_3), 40.3 (C8), 22.1 (C9), 14.9 (CH_3), 13.7 (C10). MS *m/z* (%) 291 (M^+, 47), 263 (100), 228 (90), 158 (15), 120 (21). Anal. Calc.: C 45.15; H 4.13; N 14.36%. Found: C 44.76; H 4.10; N 14.23%.

*5-Butyl-7-trichloromethyl-2-methylpyrazolo[1,5-a] pyrimidine (**3e**)*

$C_{12}H_{14}C_{13}N_3$, solid, mp 50-52 °C; MW 306.62. ^{1}H NMR (400 MHz, CDCl3): δ 0.98 (t, 3H, H11), 1.46 (sext, 2H, H10), 1.80 (quint, 2H, H9), 2.59 (s, 3H, CH3), 2.90 (t, 2H, H8), 6.56 (s, 1H, H3), 7.28 (s, 1H, H6).

^{13}C NMR (100 MHz, CDCl3): δ 161.5 (C5), 155.0 (C2), 150.8 (C3a), 141.9 (C7), 104.3 (C6), 96.3 (C3), 89.2 (CCl3), 38.3 (C8), 30.9 (C9), 22.4 (C10), 14.9 (CH3), 13.8 (C11). MS *m/z* (%) 307 (M+2, 6), 263 (100), 228 (62), 149 (14), 107 (13), 77 (17), 51 (24). Anal. Calc.: C 47.01; H 4.60; N 13.70%. Found: C 46.62; H 4.66; N 13.58%.

*7-Trichloromethyl-2-methyl-5-(3-methylpropyl) pyrazolo[1,5-a]pyrimidine (**3f**)*

$C_{12}H_{14}Cl_3N_3$, solid, mp 89-90 °C; MW 306.62. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (s, 1H, H6), 6.57 (s, 1H, H3), 2.77 (d, 2H, H8), 2.59 (s, 3H, CH_3), 2.21 (non, 8H, H9), 1.01 (d, 6H, H10). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7 (C5), 155.0 (C2), 150.8 (C3a), 141.8 (C7), 104.7 (C6), 96.4 (C3), 89.2 (CCl_3), 47.5 (C8), 28.8 (C9), 22.4 (C10); 14.9 (CH_3). MS *m/z* (%) 305 (M^+, 24), 290 (37), 272 (29), 263 (100), 228 (68), 120 (11). Anal. Calc.: C 47.01; H 4.60; N 13.70%. Found: C 46.66; H 4.67; N 13.61%.

*2-Methyl-7-phenylpyrazolo[1,5-a]pyrimidine (**3g**)*

$C_{13}H_{11}N_3$, solid, mp 124-125 °C; MW 209.25. ^{1}H NMR (400 MHz, CDCl3): δ (JH-H, Hz) 8.42 (d, 1H, H5, *J* 4.4), 7.53 (t, 3H, Ph), 8.03 (d, 2H, Ph), 6.77 (d, 1H, H6, *J* 4.4), 6.54 (s, 1H, H3), 2.51 (s, 3H, CH3). ^{13}C NMR (100 MHz, CDCl3): δ 154.8 (C2), 150.5 (C3a), 148.4 (C5), 146.0 (C7), 128.5, 129.1, 130.8, 131.1 (6C, Ph), 106.4 (C6), 96.2 (C3), 14.7 (CH3). MS m/z (%) 209 (M+, 100), 140 (7). Anal. Calc.: C 74.62; H 5.30; N 20.08%. Found: C 74.57; H 5.38; N 19.97%.

*2-Methyl-7-(4-methylphenyl)pyrazolo[1,5-a]pyrimidine (**3h**)*

$C_{14}H_{13}N_3$, solid, mp 87- 88 °C; MW 223.28. ^{1}H NMR (400 MHz, $CDCl_3$): δ (J_{H-H}, Hz) 8.41 (d, 1H, H5, *J* 4.2), 7.34 (d, 2H, Ph, *J* 8.0), 7.95 (d, 2H, Ph, *J* 8.0), 6.76 (d, 1H, H6, *J* 4.2), 6.54 (s, 1H, H3), 2.52 (s, 3H, CH_3), 2.43 (s, 3H, Ph-CH_3).^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8 (C2), 150.6 (C3a), 148.5 (C5), 146.2 (C7), 141.3, 129.2, 129.1, 128.2, (6C, Ph), 106.1 (C6), 96.1 (C3), 21.5 (CH_3, Ph), 14.7 (CH_3). MS *m/z* (%) 223 (M^+, 100), 207 (37), 115 (15). Anal. Calc.: C 75.31; H 5.87; N 18.82%. Found: C 74.99; H 6.03; N 18.71%.

*7-(4-Fluorophenyl)-2-methylpyrazolo[1,5-a]pyrimidine (**3i**)*

$C_{13}H_{10}FN_3$, solid, mp 158-160 °C; MW 227.24. ^{1}H NMR (400 MHz, CDCl3): δ (JH-H, Hz) 8.43 (d, 1H, H5, *J* 4.2), 7.23 (m, 2H, Ph, *J* 5.4), 8.10 (m, 2H, Ph, *J* 8.6), 6.77 (d, 1H, H6, *J* 4.2), 6.56 (s, 1H, H3), 2.52 (s, 3H, CH3). ^{13}C NMR (100 MHz, CDCl3,): δ (*J*C-F, Hz) 164.1 (d, 1C, Ph, *J* 252.3), 155.0 (C2), 150.5 (C3a), 148.3 (C5), 145.0 (C7), 106.1 (C6), 131.5 (d, 1C, Ph, *J* 8.5), 127.2 (d, 1C, Ph, *J* 3.5), 115.7 (d, 1C, Ph, *J* 21.8), 96.3 (C3), 14.7 (CH3). MS m/z (%) 227 (M+, 100), 158 (9), 133 (12), 120 (9), 95 (10). Anal. Calc.: C 68.71; H 4.44 ; N 18.49%. Found: C 68.10; H 4.68; N 18.26%.

*7-(4-Chorophenyl)-2-methylpyrazolo[1,5-a]pyrimidine (**3j**)*

$C_{13}H_{10}ClN_3$, solid, mp 145-147 °C; MW 243.70. ^{1}H NMR (400 MHz, $CDCl_3$): δ (J_{H-H}, Hz) 8.43 (d, 1H, H5, *J* 4.4), 7.52 (d, 2H, Ph, *J* 8.5), 8.02 (d, 2H, Ph, *J* 8.4), 6.77 (d, 1H, H6, *J* 4.4), 6.56 (s, 1H, H3), 2.52 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9 (C2), 150.5 (C3a), 148.4 (C5), 144.7 (C7), 136.9, 130.4, 129.5, 128.8, (6C, Ph), 106.2 (C6), 96.4 (C3), 14.6 (CH_3). MS *m/z* (%) 243 (M^+, 100), 208 (14), 140 (10), 113 (9), 75 (15). Anal. Calc.: C 64.07; H4.14; N 17.24%. Found: C 64.42; H 4.17; N 16.87%.

*7-(4-Bromophenyl)-2-methylpyrazolo[1,5-a]pyrimidine (**3k**)*

$C_{13}H_{10}BrN_3$, solid, mp148-150 °C; MW 288.15. ^{1}H NMR (400 MHz, $CDCl_3$): δ (J_{H-H}, Hz) 8.42 (d, 1H, H5, *J* 4.2), 7.67 (d, 2H, Ph, *J* 8.5), 7.94 (d, 2H, Ph, *J* 8.5), 6.76 (d, 1H, H6, *J* 4.2), 6.55 (s, 1H, H3), 2.51 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$,): δ 155.0 (C2), 150.6 (C3a), 148.4 (C5), 144.8 (C7), 132.0, 125.4, 130.0, 130.7, (6C, Ph), 106.2 (C6), 96.5 (C3), 14.7 (CH_3). MS *m/z* (%) 288 (MH^+, 100), 208 (27), 180 (10), 140 (12), 101 (16), 75 (25), 50 (20). Anal. Calc.: C 54.19; H 3.50; N 14.58%. Found: C 54.03; H 3.65; N 14.47%.

*2-Methyl-7-(4-nitrophenyl)pyrazolo[1,5-a]pyrimidine (**3l**)*

$C_{13}H_{10}N_4O_2$, solid, mp 171-173 °C; MW 254.24. ^{1}H NMR (400 MHz, $CDCl_3$): δ (J_{H-H}, Hz) 8.51 (d, 1H, H5, *J* 4.3), 8.26 (d, 2H, Ph, *J* 8.5), 8.41 (d, 2H, Ph, *J* 8.5), 6.82 (d, 1H, H6, *J* 4.3), 6.62 (s, 1H, H3), 2.53 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3 (C2), 150,4 (C3a), 148.8 (C5), 148.3 (C7), 123.6, 130.2, 137.1, 143.3 (6C, Ph), 106.9 (C6), 96.8 (C3), 14.6 (CH_3). MS *m/z* (%) 254 (M^+, 100), 208 (38), 63 (10). Anal. Calc.: C 61.42; H 3.96; N 22.04%. Found: C 61.09; H 3.98; N 21.92%.

*7-(Fur-2-yl)-2-methylpyrazolo[1,5-a]pyrimidine (**3m**)*

$C_{11}H_9N_3O$, solid mp 86-87 °C; MW 199.21. ^{1}H NMR (400 MHz, $CDCl_3$): δ (J_{H-H}, Hz) 8.44 (d, 1H, H5 *J* 4.55), 8.24 (d, 1H, furyl, *J* 3.52), 7.68 (d, 1H, furyl), 7.22 (d, 1H, H6, *J* 4.70), 6.69 (m, 1H, furyl, *J* 4.70), 6.55 (s, 1H, H3), 2.58 (s, 3H, CH_3) ^{13}C NMR (100 MHz, $CDCl_3$,): δ 155.0 (C2), 150.1 (C3a), 147.6(C5), 145.4(C7), 144.1, 135.1, 119.5, 112.9, (4C, furyl), 101.6 (C6), 95.9 (C3), 14.7 (CH_3). MS *m/z* (%) 199 (M^+, 100), 170 (23), 146 (10), 51 (17). Anal. Calc.: C 66.32; H 4.55; N 21.09%. Found: C 66.44; H 4.57; N 21.69%.

*2-Methyl-7-(thien-2-yl)pyrazolo[1,5-a]pyrimidine (**3n**)*

$C_{11}H_9N_3S$, solid, mp 106-108 °C; MW 215.27. ^{1}H NMR (400 MHz, $CDCl_3$): δ (J_{H-H}, Hz) 8.37 (d, 1H, H5, *J* 4.7), 8.31 (d, 1H, thienyl, *J* 3.8), 7.65 (d, 1H, thienyl, *J* 5.0), 7.21 (t, 1H, thienyl, *J* 3.8), 7.08 (d, 1H, H6, *J* 5.0), 6.53 (s, 1H, H3), 2.58 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7 (C2), 150.3 (C3a), 147.5 (C5), 139.2 (C7), 127.4, 131.2, 131.4, 132.1, (4C, thienyl), 102.8 (C6), 96.1 (C3), 14.7 (CH_3). MS *m/z* (%) 215 (M^+, 100), 162 (10), 108 (9), 69 (8). Anal. Calc.: C 61.37; H 4.21; N 19.52%. Found: C 61.74; H 4.50; N 19.81%.

*2-Methyl-7-(pyrrol-2-yl)pyrazolo[1,5-a]pyrimidine (**3o**)*

$C_{11}H_{10}N_4$, solid, mp 101-103 °C; MW 198.23. ^{1}H NMR (400 MHz, $CDCl_3$): δ (J_{H-H}, Hz) 12.32 (s, 1H, N-H), 8.32 (d, 1H, H5, *J* 4.6), 7.16 (m, 2H, pyrrol-1-yl), 6.99 (d, 1H, H6, *J* 4.6), 6.45 (s, 1H, H3), 6.42 (m, 1H, pyrrol-1-yl), 2.55 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$,): δ 154.1 (C2), 150.7 (C3a), 148.2 (C5), 136.5 (C7), 144.1, 122.5, 112.7, 110.7 (4C, pyrrol-1-yl), 100.3 (C6), 94.9 (C3), 14.4 (CH_3). MS *m/z* (%) 198 (M^+, 100), 170 (18), 145 (11), 92 (23), 52 (20). Anal. Calc.: C 66.65; H 5.08; N 28.26%. Found: C 66.45; H 5.26; N 28.12%.

*2-Methyl-7-(pyrid-2-yl)pyrazolo[1,5-a]pyrimidine (**3p**)*

$C_{12}H_{10}N_4$, solid, mp 136-138 °C; MW 210.24. ^{1}H NMR (400 MHz, $CDCl_3$): δ (J_{H-H}, Hz) 9.09, 8.80, 7.95, 7.47 (m, 4H, pyridyl) 8.55 (d, 1H, H5, *J* 4.4), 7.46 (d, 1H, H6, *J* 4.4), 6.62 (s, 1H, H3), 2.58 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$,): δ 154.9 (C2), 150.8 (C3a), 149.6 (C5), 148.3 (C7), 143.3, 125.0, 125.9, 136.5 (5C, pyridyl), 106.9 (C6), 96.2 (C3), 14.6 (CH_3). MS *m/z* (%) 210 (M^+, 100), 182 (16), 129 (11), 78 (17), 51 (21). Anal. Calc.: C 68.56; H 4.79; N 26.65%. Found: C 68.16; H 4.87; N 26.49%.

*3-Bromo-7-trichloromethyl-2-methylpyrazolo[1,5-a] pyrimidine (**4a**)*

$C_8H_5BrCl_3N_3$, solid, mp 144-146 °C; MW 329.41. ^{1}H NMR (400 MHz, $CDCl_3$) δ (*J,* Hz) 8.65 (d, 1H, H5, *J* 4.4), 7.50 (d, 1H, H6, *J* 4.4), 2.62 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) 153.6 (C5), 148.6 (C2), 147.1 (C3a), 142.7 (C7), 104.9 (C6), 88.3 (CCl_3), 87.3 (C3), 13.5 (CH_3). MS *m/z* (%) 329 (M+2, 50), 294 (100), 212 (10), 110 (14), 85 (18). Anal. Calc.: C 29.17; H 1.53; N 12.76%. Found: C 29.01; H 1.65; N 12.68%.

*3-Bromo-7-trichloromethyl-2,5-dimethylpyrazolo[1,5-a] pyrimidine (**4b**)*

$C_9H_7BrCl_3N_3$, solid, mp 136-138 °C; MW 343.44. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (s, 1H, H6), 2.74 (s, 3H, H8), 2.57 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 159.1 (C5), 153.3 (C2), 146.9 (C3a), 142.2 (C7) 106.0 (C6), 89.6 (CCl3), 85.9 (C3), 25.2 (C8), 13.5 (CH_3). MS *m/z* (%) 343 (M+2, 56), 308 (100), 226 (15), 202 (09), 157 (09), 73 (16) Anal. Calc.: C 31.48; H 2.05; N 12.24%. Found: C 46.62; H 4.56; N 13.58%.

*3-Bromo-7-trichloromethyl-2-methyl-5-propylpyrazolo[1,5-a]pyrimidine (**4d**)*

$C_{11}H_{11}N_3BrCl_3$, solid, mp 110-112 °C; MW 371.49. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (s, 1H, H6), 2.93 (t, 2H, H8), 2.57 (s, 3H, CH_3),1.87 (sex, 2H, H9), 1.06 (t, 3H, H10). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8 (C5), 153.2 (C2), 147.0 (C3a), 142.3 (C7), 105.4 (C6), 88.7 (C3), 85.9 (CCl_3), 40.6 (C8), 22.2 (C9), 13.8 (CH_3), 13.5 (C10). MS *m/z* (%) 371(M+2, 33), 356 (20), 344 (100), 308 (47). Anal. Calc.: C 35.57; H 2.98; N 11.31%. Found: C 35.18; H 3.01; N 11.20%.

*3-Bromo-2-methyl-7-phenylpyrazolo[1,5-a]pyrimidine (**4g**)*

$C_{13}H_{10}N_3Br$, solid, mp 174-176 °C; MW 288.15. ^{1}H NMR (400 MHz, $CDCl_3$): δ (J_{H-H}, Hz) 8.50 (d, 1H, H5, *J* 4.2), 7.54 (m, 3H, Ph), 8.01 (m, 2H, Ph), 6.69 (d, 1H, H6, *J* 4.2), 2.50 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1 (C2), 149.6 (C3a), 146.8 (C5), 146.6 (C7), 131.2, 130.2, 129.2, 128.6 (6C, Ph), 107.3 (C6), 85.0 (C3), 13.3 (CH_3). MS *m/z* (%) 287 (M^+, 100), 206 (19), 182 (24), 140 (44), 115 (27), 51 (30). Anal. Calc.: C 54.19; H 3.50; N 14.58%. Found: C 53.74; H 3.56; N 14.42%.

*3-Bromo-7-(4-fluorophenyl)-2-methylpyrazolo[1,5-a] pyrimidine (**4i**)*

$C_{13}H_9BrFN_3$, solid, mp 159-161 °C; MW 306.14. ^{1}H NMR (400 MHz, $CDCl_3$): δ (J_{H-H}, Hz) 8.52 (d, 1H, H5, *J* 4.4), 7.24 (m, 3H, Ph, *J* 6.9), 8.06 (m, 2H, Ph, *J* 4.9), 6.84 (d, 1H, H6, *J* 4.4), 2.51 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (J_{C-F}, Hz) 164.3 (d, 1C, Ph, *J* 252.9), 153.3 (C2), 149.4 (C3a), 146.7 (C5), 145.6 (C7), 131.6 (d, 1C, Ph, *J* 8.5), 126.3 (d, 1C, Ph, *J* 3.5), 115.9 (d, 1C, Ph, *J* 21.9), 107.1 (C6), 85.2 (C3), 13.3 (CH_3). MS *m/z* (%) 305 (M^+, 100), 224 (17), 200 (28), 173 (21), 158 (58), 133 (33), 75(16). Anal. Calc.: C 51.00; H 2.96; N 13.73%. Found: C 50.64; H 3.06; N 13.63%.

*3-Bromo-7-(4-chlorophenyl)-2-methylpyrazolo[1,5-a] pyrimidine (**4j**)*

$C_{13}H_9BrClN_3$, solid, mp 166-168 °C; MW 322.59. ^{1}H NMR (400 MHz, $CDCl_3$): δ (J_{H-H}, Hz) 8.53 (d, 1H, H5, *J* 4.4), 7.53 (d, 2H, Ph, *J* 8.6), 8.00 (d, 2H, Ph, *J* 8.7), 6.85 (d, 1H, H6, *J* 4.4), 2.51 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4 (C2), 149.4 (C3a), 146.6 (C5), 145.5 (C7), 85.2 (C3), 107.1 (C6), 129.0, 130.6, 137.5,

128.6, (6C, Ph), 13.3 (CH_3). MS *m/z* (%) 323 (M+2, 100), 242 (14), 216 (18), 189 (13), 140 (29), 113 (17), 75 (25). Anal. Calc.: C 48.40; H 2.81; N 13.03%. Found: C 48.07; H 2.80; N 12.93%.

*3-Bromo-7-(4-bromophenyl)-2-methylpyrazolo[1,5-a] pyrimidine (**4k**)*

$C_{13}H_9Br_2N_3$, solid, mp 178-179 °C; MW 367.04. ^{1}H NMR (400 MHz, $CDCl_3$): δ (J_{H-H}, Hz) 8.51 (d, 1H, H5, *J* 4.3), 7.67 (d, 2H, Ph, *J* 8.7), 7.91 (d, 2H, Ph, *J* 8.7), 6.84 (d, 1H, H6, *J* 4.3), 2.49 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2 (C2), 149.3 (C3a), 146.6 (C5), 145.3 (C7), 131.8, 130.7, 129.0, 125.8 (6C, Ph), 107.0 (C6), 85.2 (C3), 13.3 (CH_3). MS *m/z* (%) 367 (M+2, 100), 286 (15), 206 (10), 166 (13), 113 (23), 75 (21), 51 (16). Anal. Calc.: C 42.54; H 2.47; N 11.45%. Found: C 42.16; H 2.58; N 11.34%.

*3-Bromo-2-methyl-7-(4-nitrophenyl)pyrazolo[1,5-a] pyrimidine (**4l**)*

$C_{13}H_9BrN_4O_2$, solid, mp 183-185 °C; MW 333.14. ^{1}H NMR (400 MHz, $CDCl_3$): δ (J_{H-H}, Hz) 8.61 (d, 1H, H5, *J* 4.3), 8.24 (d, 2H, Ph, *J* 8.9), 8.43(d, 2H, Ph, *J* 8.9), 6.95 (d, 1H, H6, *J* 4.3), 2.53 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8 (C2), 149.5 (C3a), 149.1 (C5), 146.7 (C7), 144.1, 136.2, 130.4, 123.8 (6C, Ph), 107.9 (C6), 85.9 (C3), 13.4 (CH_3). MS *m/z* (%) 332 (M^+, 100), 286 (36), 207 (37), 74 (27), 52 (34). Anal. Calc.: C 46.87; H 2.72; N 16.82%. Found: C 46.49; H 2.86; N 16.67%.

*3-Bromo-7-(fur-2-yl)-2-methylpyrazolo[1,5-a]pyrimidine (**4m**)*

$C_{11}H_8BrN_3O$, solid, mp 133-135 °C; MW 278.11. ^{1}H NMR (400 MHz, $CDCl_3$): δ (J_{H-H}, Hz) 8.45 (d, 1H, H5, *J* 4.6), 8.11 (d, 1H, furyl, *J* 3.52), 7.65 (d, 1H, furyl, *J* 4.70), 7.18 (d, 1H, H6, *J* 4.6), 6.6 (t, 1H, furyl, *J* 4.70), 2.51 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0 (C2), 148.4 (C3a), 146.4 (C5), 145.6 (C7), 143.3, 135.4, 119.9, 112.9, (4C, furyl), 102.3 (C6), 84.8 (C3), 13,3 (CH_3). MS *m/z* (%) 277 (M^+, 100), 198 (14), 172 (28), 102 (19), 76 (22), 51 (31). Anal. Calc.: C 47.51; H 2.90; N 15.11%. Found: C 47.18; H 2.97; N 15.20%.

*3-Bromo-2-methyl-7-(thien-2-yl)pyrazolo[1,5-a] pyrimidine (**4n**)*

$C_{11}H_8BrN_3S$, solid, mp 125-128 °C; MW 294.17. ^{1}H NMR (400 MHz, $CDCl_3$): δ (J_{H-H}, Hz) 8.47 (d, 1H, H5, *J* 4.6), 8.32 (d, 1H, thienyl, *J* 3.8), 7.72 (d, 1H, thienyl, *J* 5.0),7.24 (t, 1H, thienyl, *J* 3.8), 7.16 (d, 1H, H6, *J* 5.0), 2.57 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1 (C2), 148.5 (C3a), 146.5 (C5), 139.9 (C7), 132.7, 130.6, 131.9, 127.6, (4C, thienyl), 103.7 (C6), 84.9 (C3), 13.4 (CH_3). MS *m/z* (%) 293 (M^+, 100), 214 (17), 188 (29), 161 (19), 121 (24), 63 (19). Anal. Calc.: C 44.91; H 2.74; N 14.28%. Found: C 46.72; H 2.91; N 14.17%.

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