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New Routes to Pyridino[2,3-*d*]pyrimidin-4-one and Pyridino-[2,3-*d*]triazolino[4,5-*a*]pyrimidin-5-one Derivatives

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Abstract: 2-Thioxopyrimidinyl-5-(N,N-dimethylamino)formamidine (**5**) and 1,3-diphenyltriazolo[3,4-d]pyrimidinyl-N,N-dimethylformamidine (**14**) were prepared by condensation of 6-amino-2-thioxo-1,3-dihydropyrimidin-4-one (**2**) and 7-amino-1,3-diphenyl-1,2,4-triazolo[4,3-*a*]pyrimidin-4-one (**13**) with dimethylformamide dimethyl-acetal (DMFDMA). Compound **5** reacts with acetophenone and 2-acetylthiophene to give the 2-thioxo-1,3-dihydropyridino[2,3-d]pyrimidin-4-ones **3a** and **3b,** respectively. Compounds **3a,b** react with hydrazonoyl halides **6,7** to give pyridino[2,3-*d*]triazolo[4,5-*a*]pyrimidin-4-ones **11a-d** and not the isomeric structures **12a-d**. Formamidines of type **14** react with ethyl cyanoacetate, malononitrile and benzoyl acetonitrile to give the 1,3-diphenyl-3a-hydropyridino[2,3-*d*]1,2,4-triazolo[4,5-*a*]pyrimidin-4-one derivatives **15a,b** and **18**, respectively. The structures of the newly synthesized compounds are established on the basis of chemical and spectroscopic evidences as well as their synthesis by alternative methods.

Keywords: Enaminones, Pyridino[2,3-*d*]pyrimidin-4-one, Formamidine, Dimethyl-formamide dimethylacetal, Hydrazonoyl halides.

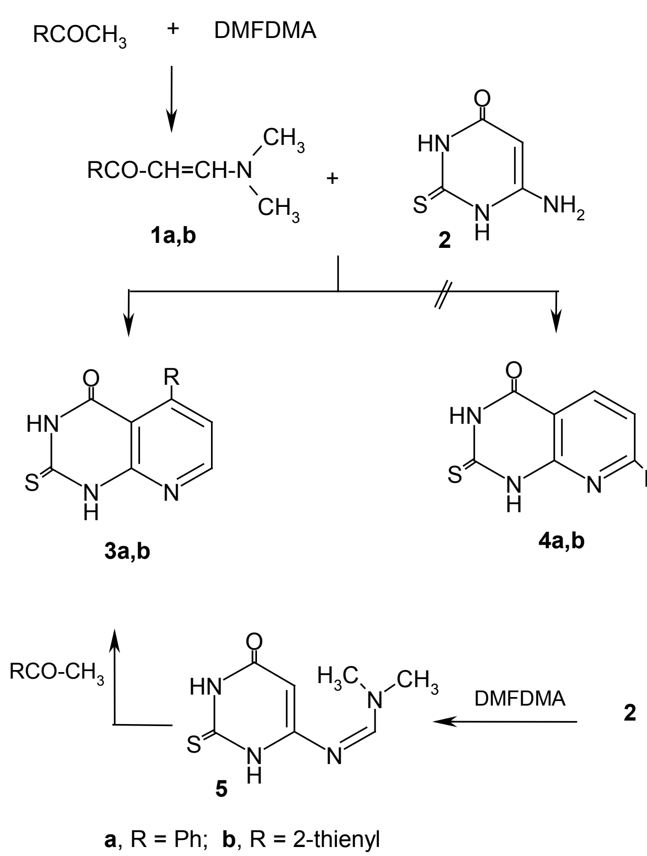
Introduction

Azoloazine derivatives form a very interesting class of compounds because of their significant biological and pharmaceutical activities and their chemistry is consequently now receiving considerable attention [1-4]. As part of our studies aimed at developing simple and efficient syntheses of polyfunctional heteroaromatics from readily obtained starting materials [5-10]. We now wish to report the reaction of pyridino[2,3-*d*]pyrimidines **3** with hydrazonoyl halides **6,7** to give novel functionalized heterocycles having pyridine rings condensed with other important heterocycles such as pyrimidines and triazolopyrimidines. In many cases, however, the exact structure of the reaction products could not be established unequivocally, because several close similar isomeric products could conceivably be formed. In this paper, we report the synthesis of heterocyclic compounds **3**, **5, 11**, **14**, **15** and **18** and the confirmation of the structures of the resulting products by spectroscopic data as well as their synthesis by alternative methods. The newly synthesized compounds appear to be promising substrates for further chemical transformations as well as biological activity evaluations.

Results and Discussion

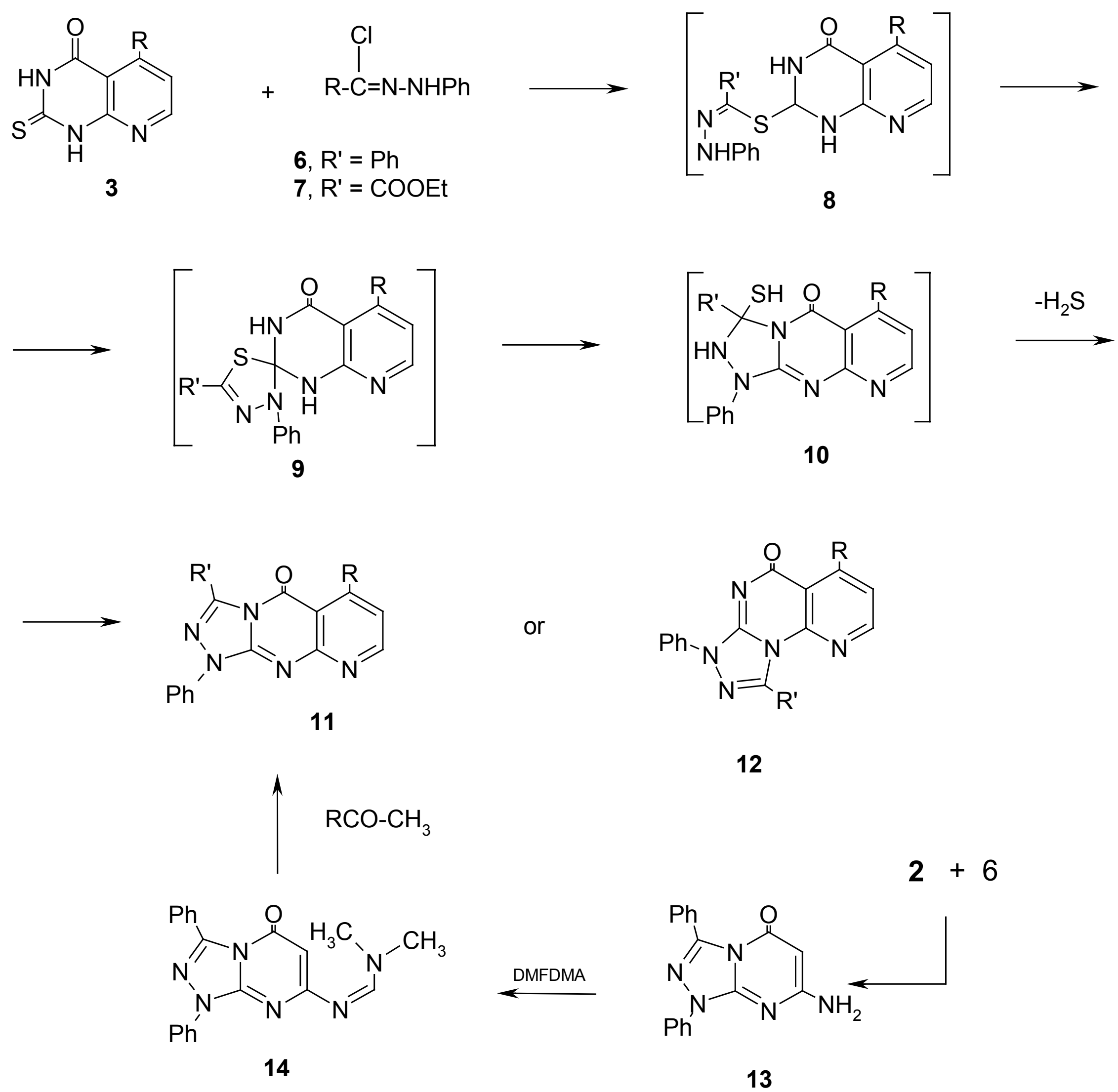
Enaminones **1a,b** were prepared by reaction of dimethylformamide dimethylacetal (DMFDMA) with acetophenone and 2-acetylthiophene in refluxing dioxane (Scheme 1), as previously described [11].

Scheme 1



Enaminones **1a,b** condensed readily with 6-amino-2-thioxopyrimidin-4(*3H*)one (**2**) [12] in boiling acetic acid to give either pyridino[2,3-*d*]pyrimidine derivatives **3a,b** or the isomeric structures **4a,b** in high yields (Scheme 1). The ^{1}H-NMR spectra of the resulting products displayed four signals readily recognizable as arising from two CH (δ 7.91, 8.63) and two NH groups (δ 12.62, 13.17), along with the multiplet in the aromatic region. Their IR spectra revealed the absence of the bands corresponding to the amino group. Elemental analysis and mass spectra agreed equally with both structures **3** and **4.** These data alone cannot determine the exact structures of the resulting products therefore conclusive evidence for the structures was obtained by synthesis of **3a,b** *via* reactions of N,N-dimethylaminoformamidine **5** with acetophenone and 2-acetylthiophene, respectively (Scheme 1).

Scheme 2



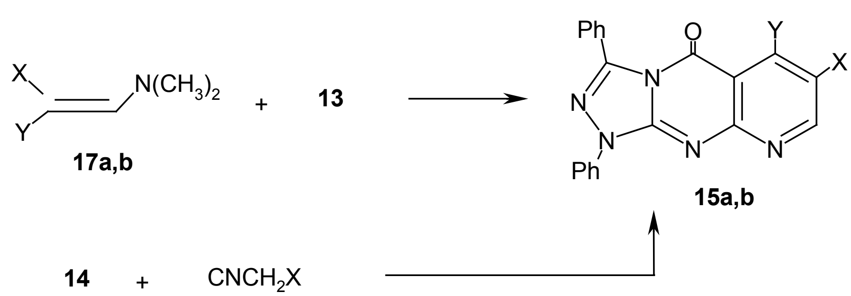
11a, R = R' - Ph **11b**, R = 2-thienyl, R' = Ph
11c, R = Ph, R' = COOEt **11d**, R = 2-thienyl, R' = COOEt

The required intermediate **5** was obtained by condensation of **2** with DMFDMA in boiling dioxane (Scheme 1). The ^{1}H-NMR spectrum of **5** displayed six singlets recognizable as arising from the two methyls (δ 2.99, 3.11), the CH=N- (δ 5.24), the CH of the pyrimidine ring at δ 8.14 and two NH groups at δ 11.61 and 11.79 ppm. Structure **5** was further confirmed by its mass spectrum, which gave an intense molecular ion peak at m/z 198.

Treatment of **3a,b** with hydrazonoyl chlorides **6** and **7** in boiling chloroform in the presence of triethylamine led to the formation of either **11a-d** or the isomeric structures **12a-d** (Scheme 2). Structures **11a-d** could be established for these products based on their alternate syntheses. For example, formamidine **14** reacts with acetophenone in boiling glacial acetic acid to give a product which was found to be identical in all respects (mp, mixed mp, IR, ^{1}H-NMR) with structure **11a**. The structure assignments of **11a-d** were also supported by spectroscopic data. For example, the ^{1}H-NMR spectra revealed the absence of the signals corresponding to the N,N-dimethylaminoformamidine group, instead it showed two doublets at 7.91, 8.63 corresponding to protons at positions 7,8 in the pyridine ring. Compound **14** was obtained by condensation of 7-amino-1,3-diphenyl-1,2,4-triazolo[4,3-*a*]pyrimidin-5-one (**13**), prepared *via* dipolar cycloaddition of **2** with hydrazonoyl halide **6** in chloroform in the presence of triethylamine, with DMFDMA (Scheme 2).

The structure of **14** was confirmed by elemental analysis and spectroscopic data (IR, ^{1}H-NMR, ^{13}C-NMR, mass spectra). For example, the mass spectrum gave an intense molecular peak at m/z 358. The ^{1}H-NMR spectrum showed the characteristic signals of N,N-dimethylformamidine group at δ 3.14 (s, 3H), 3.15 (s, 3H), 5.66 (s, 1H) in addition to a multiplet in the aromatic region. The ^{13}C-NMR spectra of **14** revealed two sp^3 carbons, which can be assigned to the two methyl groups at δ 35.61, and 41.80 and a signal at δ 91.80 assigned to the N=CH, in addition to the carbon atoms in the aromatic system. The versatile compound **14** can also allow the synthesis of condensed pyridino[2,3-d]triazolo[4,5-a]pyrimidin-4-ones. To demonstrate its potential, **14** was reacted with ethyl cyanoacetate and malononitrile in boiling glacial acetic acid to yield products of condensation **15a,b** by elimination of dimethylamine and then cyclization (Scheme 3).

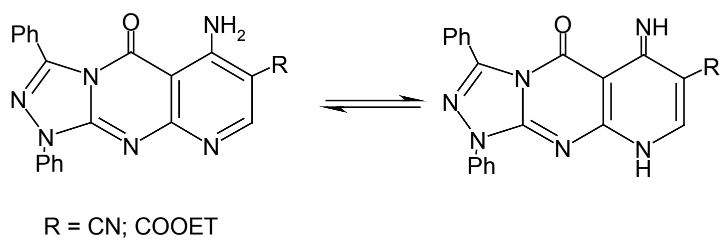
Scheme 3



	X;	Y
a	COOEt;	NH_2
b	CN;	NH_2

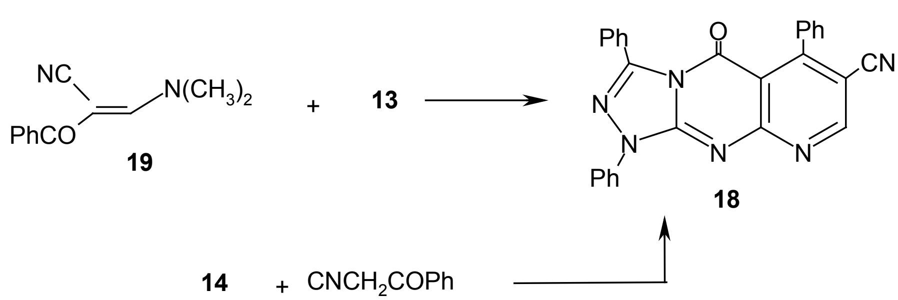
The mass spectra of the products showed intense peaks at m/z 426 and 379 assignable to the molecular ion peaks of the compounds **15a** and **15b**, respectively. The ^{1}H-NMR spectrum of **15a** indicated the disappearance of the protons from the N,N-dimethylformamidine group, and instead showed a triplet at δ 1.29 (3H) and a quartet at 4.20 ppm (2H), assigned to ethoxycarbonyl group. The structures of the products were also confirmed by their alternative synthesis via reaction of **13** with enaminones **17a** and **17b,** respectively. Despite the fact that heterocyclic amines are well known to exist preferentially in the amino rather than the imine form, compounds **15a** and **15b** exist mainly, at least in DMSO solution, in the imine form (Scheme 4). This was confirmed by their ^{1}H-NMR spectra which revealed two signals for two NH groups at about δ 5.68 and 11.73 ppm (1H each) which disappeared on shaking with deuterium oxide.

Scheme 4



Compound **14** also reacts under similar conditions with benzoylacetonitrile to give the condensation product **18** by elimination of dimethylamine and water (Scheme 5). The mass spectrum of the product gave an intense peak at m/z 440 corresponding to the expected molecular ion peak of **18**. The structure was also confirmed by its alternative synthesis from **19** and **13** (Scheme 5).

Scheme 5



In conclusion, the have reported the preparation of readily obtainable formamidines that are valuable precursors for the synthesis of a variety of heteroaromatics of potential interest for biological evaluation.

Experimental

General

All melting points are uncorrected. IR spectra (KBr pellets) were recorded with a Pye Unicam SP-3000 IR spectrophotometer. NMR spectra were determined on a Varian Gemini 200 spectrometer using DMSO-d_6 as solvent and TMS as internal standard; chemical shifts are reported in δ units (ppm). Mass spectra were measured at 70eV using a Shimadzu GCMS-QP 1000 EX instrument. Microanalyses were performed on a Perkin-Elemer 2400 CHN Elemental Analyzer at the University of Cairo Microanalytical Center. Compounds **6** [13], **7** [14], **13** [15] were prepared following published procedures. Unless stated otherwise standard workups consisted of allowing the reaction mixtures to cool, collecting the precipitates formed and recrystallizing them from dimethylformamide (DMF). The analytical and spectral data of compounds prepared is summarized in Tables 1 and 2.

General Procedures for the Synthesis of 2-Thioxo-1,3-dihydropyridino[2,3-d]pyrimidin-4-ones (**3a,b**).

Method A. Enaminones **1a,b** (0.001 mol) were refluxed with **2** (1.43 g, 0.001 mol) in glacial acetic acid (20 mL) for 2h to give compounds **3a,b** after the standard workup.

Method B. Formamidine **5** (1.98 g, 0.001 mol) was refluxed with 2-acetylthiophene (1.26 g, 0.001 mol) or acetophenone (1.20 g, 0.001 mol) in glacial acetic acid (10 mL) for 2h. The products were identical in all respects (mp, mixed mp, IR) to those prepared by method A.

Synthesis of 2-thioxopyrimidinyl-5-(N,N-dimethylamino)formamidine (**5**)

A mixture of **2** (1.47 g, 0.001 mol) and DMFDMA (1.19 g, 0.012 mol) was refluxed in dioxane (25 mL) for 3h. The reaction mixture was then cooled to room temperature and the product was collected and crystallized from DMSO.

General Procedure for the Synthesis of Pyridino[2,3-d]1,2,4-triazolo[4,3-a]pyrimidin-4-ones (**11a-d**)

Method A: To a mixture of compound **3** (0.005 mol) and hydrazonoyl halides **6,7** (0.005 mol) in chloroform (40 mL) triethylamine (0.7 mL, 0.005 mol) was added. The reaction mixture was refluxed until the hydrazonoyl halides disappeared (4-6 h) as indicated by TLC analysis. The solvent was evaporated under reduced pressure and the residue was treated with methanol (10 mL).

Method B: A mixture of formamidine **14** (1.79 g, 0.005 mol) and 2-acetylthiophene (1.26 g, 0.005 mol) or acetophenone (1.2 g, 0.005 mol) was refluxed in acetic acid for 3 h to give **11a,b,** identical in all respects (mp, mixed mp, IR) to that prepared by Method A.

Synthesis of 1,3-diphenyltriazolo[3,4-d]pyrimidinyl-N,N-dimethylformamidine (**14**)

7-Amino-1,3-diphenyl-1,2,4-triazolo[4,3-*a*]pyrimidine-5-one (**13**, 1.51 g, 0.005 mol) was refluxed in DMFDMA (10 mL) for 3h.

General Procedure for the Synthesis of Pyridino[2,3-d]triazolo[4,5-a]pyrimidin-5-ones (**15,18**).

A solution of **14** (1.79 g, 0.005 mol) and a nitrile compound (0.005 mol) was refluxed in acetic acid (10 mL) for 2h.

Table 1. Analytical data of the synthesized compounds

Compd. no.	**Color**	**Yield (%)**	**m.p. °C solvent**	**Mol. formula (Mol. Wt)**	**Analysis Calcd (Found)**			
					C	**H**	**N**	**S**
3a	yellowish	75	260-261	$C_{13}H_9N_3OS$	61.15	3.55	16.47	12.54
	white		DMF	255.10	61.40	3.71	16.53	12.59
3b	yellow	80	254-255	$C_{11}H_7N_3OS_2$	50.56	2.70	16.09	24.51
			DMF	261.08	50.54	2.52	16.37	24.45
5	yellow	85	339-341	$C_7H_{10}N_4OS$	42.40	5.08	28.28	16.15
			DMSO	198.11	42.49	5.15	28.36	16.33
11A	colorless	78	281-282	$C_{26}H_{17}N_5O$	75.15	4.12	16.86	
			DMF	415.19	75.25	4.23	17.06	
11B	yellowish	80	287-289	$C_{24}H_{15}N_5OS$	68.38	3.58	16.62	7.59
	white		DMF	421.17	61.31	3.74	16.52	7.36
11C	yellow	76	286-288	$C_{23}H_{17}N_5O_3$	67.12	4.16	17.03	
			DMF	411.19	67.25	4.08	17.29	
11D	yellow	75	216-218	$C_{21}H_{15}N_5O_3S$	60.41	3.62	16.78	7.67
			DMF	417.17	60.26	3.40	16.63	7.82
14	colorless	90	208-209	$C_{20}H_{18}N_6O$	67.00	5.06	23.46	
			DMF	358.20	67.24	5.35	23.58	
15a	yellow	75	350-352	$C_{23}H_{18}N_6O_3$	64.76	4.25	19.71	
			DMF	426.20	64.73	4.21	19.86	
15b	colorless	80	335-337	$C_{21}H_{13}N_7O$	66.46	3.45	25.85	
			DMF	379.17	66.78	3.62	25.70	
18	yellowish	82	327-328	$C_{27}H_{16}N_6O$	73.61	3.66	19.09	
	white		DMF	440.19	73.79	3.51	19.24	

Table 2. Spectroscopic data of synthesized compounds

Compd. no.	IR (ν/cm^{-1})	M$^+$	^{1}H-NMR (δ/ppm)
3a	1686 (CO), 3255 (NH)	255	7.56-7.59 (m, 3H, aromatic-H), 7.91 (d, 1H, pyridine), 8.18-8.22 (m, 2H, aromatic-H), 8.63 (d, 1H, pyridine), 12.62 (s, 1H, NH), 13.17 (s, 1H, NH).
3b	1680 (CO), 3343 (NH)	261	7.25-9.22 (m, 5H, aromatic-H), 12.86 (s, 1H, NH), 13.32 (s, 1H, NH).
5	1648 (CO), 3256 (NH)	198	2.99 (s, 3H, CH_3); 3.11 (s, 3H, CH_3), 5.24 (s, 1H, N=CH), 8.14 (s, 1H, pyrimidine), 11.61 (s, 1H, NH), 11.79 (s, 1H, NH).
11a	1710 (CO)	415	7.88 (d, 1H, pyridine); 7.56-8.00 (m, 15H, aromatic-H); 8.63 (d, 1H, pyridine).
11b	1702 (CO)	421	7.23-8.49 (m, 13H, aromatic-H); 7.91 (d, 1H, pyridine); 8.73 (d, 1H, pyridine).
11c	1715 (CO) 1720 (ester CO)	411	1.42 (t, J = 7Hz, 3H, CH_3); 4.25 (q, J = 7Hz, 2H, CH_2); 7.21-8.24 (m, 10H, aromatic-H); 7.72 (d, 1H, pyridine), 8.50 (d, 1H, pyridine).
11d	1700(CO), 1715 (ester CO)	417	1.41 (t, J = 7 Hz, 3H, CH_3), 4.28 (q, J = 7 Hz, 2H, CH_2), 7.73 (d, 1H, pyridine-H), 5.45-8.11 (m, 8H, aromatic-H), 8.55 (d, 1H, pyridine-H).
14	1702 (CO)	358	3.14 (s, 3H, CH_3), 3.15 (s, 3H, CH_3), 5.66 (s, 1H, N=CH), 7.21-8.40 (m, 10H, aromatic H), 8.59 (s, 1H, pyrimidine H-6).
15a	1690 (CO), 1715 (ester CO)	426	1.29 (t, J=7Hz, 3H, CH_3), 4.20 (q, J= 7Hz, 2H, CH_2), 5.85 (s, 1H, NH), 7.46-8.10 (m, 10H, aromatic-H), 8.92 (s, 1H, pyridine), 11.78 (s, 1H, NH).
15b	1720 (CO), 2229 (CN), 3193, 3400 (2 NH)	337	5.68 (s, 1H, NH), 7.47-8.17 (m, 10H, aromatic-H), 8.66 (s, 1H, pyridine), 11.73 (s, 1H, NH).
18	1728 (CO), 2221 (CN)	440	7.48-8.29 (m, 15H, aromatic-H); 9.15 (s, 1H, pyridine)

^{13}C-NMR data (δ, DMSO-d_6): (**5**): 167.27 (CO), 160.94 (CS), 163.35, 158.31, 96.48 (N=CH), 36.17 (CH_3), 14.48 (CH_3); (**14**): 168.37 (CO), 158.82, 157.44, 148.89, 145.72, 137.78, 131.17, 129.89, 129.65, 128.23, 127.40, 127.00, 121.44, 91.80 (N=CH), 41.80 (CH_3), 35.61 (CH_3); (**15a**): 165.44 (CO), 158.33(CO), 158.58, 151.60, 149.89, 146.59, 137.91, 133.32, 131.03, 129.44, 129.33, 127.74, 122.89, 116.62, 87.69, 80.78, 77.22, 62.79 (CH_2), 15.95(CH_3)

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Sample availability: Samples not available.