





- Used in the treatment of brain tumors glioblastoma or anaplastic astrocytoma
- Alkylating agent Methylates N-7 or O-6 guanine most often
 - Triggers cell death
 - Diffuses through the blood brain barrier readily
 - Metabolized to MTIC, releases diazomethane (active methylating agent)
- Recently reported to be an effective methylation/cyclopropanation reagent
- See <u>Marko Nesic DOTW 7/3/2020</u>



Mechanism for _____ diazomethane release



Utility in -----



Angew. Chem. Int. Ed. 2020, 59 (5), 1857–1862. https://doi.org/10.1002/anie.201911896.





Differential Scanning Calorimetry (DSC) experiments



vendor	reported HPLC purity (%)	average onset (°C)	average energy release (J/g)
1	97	169	-1394
2	>99	108	-1406
3	>98	171	-1395
4	>98	176	-1445
5	>99	181	-1439

" ... the DSC data obtained for the first lot received showed rapid decomposition beginning at approximately 170 °C, well below the reported melting point of 212 °C. This single exothermic decomposition event releases more than 1430 J/g of energy and a maximum heat flow of >80 W/g. Given that the anticipated reaction conditions were 60 °C or greater, together with these results, the decision was made to not allow scientists to pursue TMZ for the esterification reaction until a thorough process safety evaluation was completed."



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50 cm	40 cn	n 3	0 cm	20 cm	10 cn
entry	50 cm (49 J)	40 cm (39 J)	30 cm (29 J)	20 cm (20 J)	10 cm (9.8 J
1	yes	yes	yes	yes	yes
2	yes	yes	yes	yes	no
3	no	yes	yes	yes	yes
4	yes	no	yes	no	no
5	yes	yes	yes	yes	no
6	yes	no	yes	yes	no

yes = decmposition no = material recovered



Org. Process Res. Dev. 2021, XXXX, XXX, XXX-XXX https://doi.org/10.1021/acs.oprd.1c00206.

Fallhammer





Accelerating Rate Calorimetry (ARC) experiments



UN test series 2 - inclusion into Class 1

test	experiment design	intended measurement	failure definition	result
UN 2-inch gap test	TMZ separated 2 inches from a booster inside a steel tube; detonated	detonative shock sensitivity	tube fragmentation or puncturing	pass
Koenen test	TMZ placed in a unit with small oriffice; placed in a closing device; heated by propane torch	thermal sensitivity in confinement	tube fragmentation/ damage to closing device	pass
Time/Pressure Test	Measure pressure/time as TMZ is ignited under confinement	effect of ignition in confinement	pressure increases from 690 kPa to 2070 kPA in under 30 ms	fail

UN test series 3 - thermal stability and transportation hazards

test	experiment design	intended measurement	failure definition	result
Bureau of Explosives Impact machine	similar to fallhammer (10 cm - 3.63 kg)	impact sensitivity	compound detonates	pass
BAM friction sensitivity	up to 360 N applied to TMZ by frictional stimuli	friction sensitivity	explosion observed at or below 80 N	pass
thermal stability	TMZ heated to 75 C for 48h, or until explosion	thermal stability	explosion or decomposition	pass
small-scale burning	kersone/sawdust bed ignition below 10/100g samples of TMZ	response to fire	explosion	pass



Koenan test - after



2-inch gap test - after





Conclusion

<5g-500g = medium hazard, >500g = high hazard
TMZ is provisionally deemed to be a class 1 explosive until series
6 tests (kilo scale) can assign a division or reverse this designation
Raw thermal stability data should be presented when making claims on compound stability in the future

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